C. J. Mieny, U. Mennen: Principles of Surgical Patient Care - Volume I

Chapter 3: Normal Postoperative Care and Complications

Chapter 3.1: Metabolic Response to Trauma

C. J. Mieny, G. A. G. Decker

Definition of Trauma

Any stress which includes injury, surgery, anesthesia, burns, vascular occlusion, dehydration, starvation, sepsis and shock will initiate the metabolic response to trauma.

Following trauma, the body responds locally by inflammation and by a general response which conserves fluid and provides energy for repair.

Stages of the Response

The metabolic response to trauma was divided into an ebb and flow phase by Cuthbertson. The ebb phase corresponds to the period of severe shock characterized by depression of enzymatic activity and oxygen consumption.

A flow phase can be divided into:

- a catabolic phase with fat and protein mobilization associated with increased urinary nitrogen excretion and weight loss, and

- an anabolic phase with restoration of fat and protein stores, and weigth gain.

Factors Influencing the Response

The magnitude of the metabolic response depends on the degree of trauma and the concomitant contributory factors such as drugs, sepsis and underlying systematic disease. The response will depend on the age and sex of the patient, the underlying nutritional state, the timing of treatment and the type and effectiveness of the treatment. The more severe the injury, the greater the metabolic response. Burns cause a relatively greater response than other injuries of comparable extent probably because of the propensity for greater continued volume depletion and heat loss. In burns units the ambient temperature is usually raised to between 30 and 32 °C to reduce the increased metabolism which is directed at maintaining body temperature.

Sepsis potentiates the response by prolonging the catabolic phase. Underlying conditions such as deep vein thrombosis and pulmonary emboli also prolong and potentiate the response.

The metabolic response seems to be less marked in children and the elderly and in the premenopausal female. Starvation and nutritional depletion also modify the response. Patients in poor nutritional status have a smaller metabolic response to trauma than well-nourished

patients.

Hypovolaemia due to external and internal shifts of extracellular fluids, and changes in plasma osmolality, stimulate catecholamines which in turn trigger the neuroendocrine response which plays such an important role in volume and electrolyte conservation and protein, fat and carbohydrate catabolism. Early fluid and electrolyte replacement, and parenteral surgical nutrition administering amino acids to injured patients losing nitrogen at an accelerated rate, and fat and carbohydrates to counter caloric deficits may modify the response significantly. However, the availability of the methods should not distract the surgeon from his primary responsibility of adequate resuscitation to shut off the hypovolaemic stimulus which triggered the neuro-endocrine response.

Endocrine Mediators of the Response to Trauma

The hypothalamus is the highest level of integration of the stress response. The major efferent pathways of the hypothalamus are endocrine via the pituitary and the efferent sympathetic and parasympathetic systems.

Pain receptors, osmoreceptors, baroreceptors and chemoreceptors stimulate or inhibit ganglia in the hypothalamus to induce sympathetic nerve activity. The neural endplates and adrenal medulla secrete catecholamines. Pain stimuli via the paint receptors also stimulate secretion of endogenous opiates, B-endorphin and enkephalin (precursor fragments of the ACTH molecule) which modifies the response to pain and reinforces the catecholamine effects.

Hypotension, hypovolaemia and hyponatraemia stimulate secretion of vasopressin, the antidiuretic hormone ADH from the posterior pituitary, aldosterone from the adrenal cortex, and renin from the juxtaglomerular apparatus of the kidney.

Hypovolaemia stimulates receptors in the right atrium and hypotension stimulates receptors in the carotid artery. This results in activation of paraventricular hypothalamic nuclei which secrete releasing hormone from the median eminence into capillary blood which stimulates the anterior pituitary to secrete adrenocorticotrophin (ACTH). ACTH stimulates the adrenal cortex to secrete cortisol. Changes in glucose concentration influence the release of insulin from the B cells of the pancreas, and high amino-acid levels the release of glucagon from the A cells.

Toxins derived fromj necrotic tissue or bacteria, either directly or via activation of the complement system, stimulate platelets, mast cells and basophils to secrete histamine and serotonin.

The short-lived fragments of the complement cascade, C3a and C5a, stimulate macrophages to secrete interleukin-1 (IL-1) and its active circulating cleavage product proteolysis inducing factor (PIF) which in turn stimulates T4 helper cells to produce interleukin-2 (IL-2).

Bradykinin, a vasoactive nonapeptide is derived from bradykininogen in response to kallikrein. Bradykinin in turn is activated by factor XII (Hageman factor).

Eicosanoids

These compounds, derived from eicosapolyenoic fatty acids, comprise the prostanoids and leukotrienes (LT). Prostanoids include the prostaglandins (PG), prostacyclins (PGI) and thromboxanes (TX). The term prostaglandins is often used loosely to include all prostanoids.

Eicosanoids are synthesized from arachidonic acid which has been synthesized from phospholipids of damaged cell walls, white blood cells and platelets, by the action of phospholipase A2. Lipoxygenase, derived from white cells and macrophages, convert arachidonic acid to leukotrienes (LTB4, LTC4 and LTD4). Cyclo-oxygenase converts arachidonic acid to prostanoids, the precursors of prostaglandin (PG), prostacyclins (PGI) and thromboxanes (TX).

The Early Hyperdynamic Stage

The cardiac index rises to more than 3.5 litres/minute/m^2 after severe trauma or infection in those patients who are able to respond adequately. This hyperdynamic state elevates the resting energy expenditure to more than 20% above normal. In an inadequate response with a cardiac index lower than 2.5 litres/minute/m^2, oxygen consumption may fall to values less than 100 mL/minute/m^2 (normal 120-160 mL/min/m^2). Endotoxin and anoxia may injure cells and limit their ability to utilize oxygen for oxidative phosphorylation.

The amount of ATP synthesized by an adult is more than 50 kg per day. However, there is no reservoir of ATP or creatine phosphate, therefore cellular injury and lack of oxygen result in rapid deterioration of processes requiring energy. In shock the oxidation reduction (redox) potential declines and conversion of pyruvate to acetyl co-enzyme A for entry into the Krebs' cycle is inhibited and lactate is produced. Because of anaerobic glycolysis only 2 ATP equivalents instead of 34 are produced from one mole of glucose in the Krebs' cycle. Lactate which is normally reconverted to glucose in the Cori cycle in the liver, accumulates because of impaired hepatic gluconeogenesis, causing a severe metabolic acidosis.

The Inflammatory and Immunological Response to Trauma

Tissue injury activates an inflammatory and immune defence response. These responses are mediated along two pathways: activation of the complement cascade system with generation of the anaphylatoxins C3a and C5a which is responsible for aggregation of neutrophils and activation of basophils, mast cells and platelets to secrete histamine and serotonin which alter vascular permeability and are vasoactive.

The anaphylatoxins also stimulate macrophages to secrete IL-1 and PIF which cause proteolysis and lipolysis with fever. IL-1 activates T4 helper cells to produce interleukin-2 which enhances cell-mediated immunity. IL-1 and PIF are potent mediators stimulating cells of the liver, bone marrow, spleen and lymph nodes to produce acute-phase proteins which include complement, fibrinogen, alpha2-macroglobulin and other proteins required for the defence mechanisms.

Activation of factor XII (Hageman factor) stimulates kallikrein to produce bradykinin

from bradykininogen which also affects capillary permeability and vaso-activity. A combination of these reactions causes the inflammatory response.

The leukotrienes and prostanoids derived from the arachidonic acid cascade also play an important role. The leukotrienes (LTB4, LTC4 and LTD4) cause vasocontriction, increased capillary permeability and bronchoconstriction. The prostanoids (prostaglandins of E and F series, prostacyclin (PGI2) and thromboxane synthesized from arachidonic acid by cyclo-oxygenase (in TXA2) endothelial cells, white cells and platelets also cause vasoconstriction (TXA2, PGF1) but vasodilatation (PGI1, PGE1 and PGE2) as well. TXA2 activates and aggregates platelets and white cells and PGI2 and PGE1 inhibits white cells and platelets.

The endogenous opioids, B endorphin and enkephalin play a role as well in the activation of the immune defence systems.

Water and Salt Retention

The oliguria which follows injury is a consequence of the release of ADH and aldosterone. Secretion of antidiuretic hormone (ADH) from the supraoptic nuclei in the anterior hypothalamus is stimulated by volume reduction and increased osmolality. The latter is mainly due to an increased sodium content of the extracellular fluid. Volume receptors are located in the atria and pulmonary arteries and osmoreceptors are located near ADH neurons in the hypothalamus. ADH acts mainly on the collecting tubules of the kidney but also on the distal tubules to promote reabsorption of water.

Aldosterone secretion is increased by several mechanisms. The renin-angiotensin mechanism is the most important. When the glomerular arteriolar inflow pressure falls, the juxtaglomerular apparatus of the kidney secretes renin which acts with angiotensinogen to form angiotensin I. This is converted to angiotensin II, a substance which stimulates production of aldosterone by the adrenal cortex. Reduction in sodium concentration stimulates the macula densa, a specialized area in the tubular epithelium adjacent to the juxtaglomerular apparatus, to activate renin release. An increase in plasma potassium concentration also stimulates aldosterone release. Volume decrease and a fall in arterial pressure stimulates release of ACTH via receptors in the right atrium and the carotid artery.

Aldosterone acts mainly on the distal renal tubules to promote reabsorption of sodium and bicarbonate and increased excretion of potassium and hydrogen ions. Aldosterone also modifies the effects of catecholamines on cells, thus affecting the exchange of sodium and potassium across all cell membranes. The release of large quantities of intracellular potassium into the extracellular fluid may cause a significant rise in serum potassium especially if renal function is impaired. Retention of sodium and bicarbonate may produce metabolic alkalosis with impairment of the delivery of oxygen to the tissues. After injury urinary sodium excretion may fall to 10-25 mmol/24 hours and potassium excretion may rise to 100-200 mmol/24 hours.

Atrial natriuretic factor (ANF) or atriopeptin is a hormone produced by the atria, predominantly the right atrium of the heart, in response to an increase in vascular volume. ANF produces an increase in glomerular filtration and pronounced natriuresis and diuresis. It also produces inhibition of aldosterone secretion which minimizes kaliuresis and causes

suppression of ADH release.

Prior to the discovery of ANF it was suggested that a hormone, a third factor, was secreted following distension of the atria which complemented the activity of two known regulators of blood pressure and blood volume: the hormone aldosterone and filtration of blood by the kidney.

ANF has also highlighted the heart's function as an endocrine organ. ANF has great therapeutic potential in the treatment of intensive-care patients who are undergoing parenteral therapy.

The Catabolic Phase of Carbohydrate, Fat and Protein Metabolism

Carbohydrates

The blood-glucose concentration of patients often increases to twice normal after serioud injury. Glucose is mobilized from stored glycogen in the liver by catecholamines, glucocorticoids and glucagon. Early on the insulin blood levels are suppressed (usually lower than 8 units/mL) by the effect of adrenergic activity of shock on degranulation of the B cells of the pancreas. Glucose can be derived from liver glycogen for 12 to 18 hours only. Thereafter gluconeogenesis is stimulated by corticosteroids and glucagon. The suppressed insulin favours the release of amino acids from muscle which are then available for gluconeogenesis. Growth hormone inhibits the effect of insulin on glucose metabolism.

Thyroxine also accelerates gluconeogenesis but T4 and T3 levels are usually low or low-normal in severely injured patients.

As blood glucose rises during the phase of hepatic gluconeogenesis, blood insulin concentration rises, sometimes to very high levels. Provided that the liver circulation is maintained, gluconeogenesis will not be suppressed by hyperinsulinaemia or hyperglycaemia, because the accelerated rate of glucose production in the liver is required for clearance of lactate and amino acids which are not used for protein synthesis. This period of breakdown of muscle protein for gluconeogenesis and the resultant hyperglycaemia characterize the catabolic phase of the metabolic response to trauma.

Fat

The principle source of energy following trauma is adipose tissue. Lipids stored as triglycerides in adipose tissue are mobilized when insulin falls below 25 units/mL. Because of the suppression of insulin release by the catecholamine response after trauma, as much as 200-300 g of fat may be broken down daily after severe trauma. Tumour necrosis factor (cachectin) and possibly IL-1 play a role in the mobilization of fat stores.

Catecholamines and glucagon activate adenyl-cyclase in the fat cells to produce cyclic adenosine monophosphate (cyclic AMP). This activates lipase which promptly hydrolyzes triglycerides to release glycerol and fatty acids. Growth hormone and cortisol play a minor role in this process as well. Glycerol provides substrate for gluconeogenesis in the liver which

derives energy by beta-oxidation of fatty acids, a process inhibited by hyperinsulinaemia.

Ketones are released into the circulation and are oxidized by all tissue except the blood cells and the central nervous system. Ketones are watersoluble and will pass the blood brain barrier freely permitting rapid central nervous system adaptation to ketone oxidation.

Free fatty acids provide energy for all tissues and for hepatic gluconeogenesis. Carnitine, synthesized in the liver, is required for the transport of fatty acids into the cells.

Amino Acids

The intake of protein by a healthy adult is between 80 and 120 g (13-20 g of nitrogen) per day. In the absence of an exogenous source of proteinj, amino acids are principally derived from the breakdown of skeletal muscle protein. Following trauma or sepsis the release rate of amino acids increase by three to four times. This process appears to be induced by proteolysis inducing factor (PIF) which has been shown to increase by as much as eight times in these patients.

Cortisol, glucagon and catecholamines also play a role in this reaction. The mobilized amino acids are utilized for gluconeogenesis or oxidation in the liver and other tissues, but also for synthesis of acute-phase proteins required for immuno-competence, clotting, wound healing and maintenance of cellular function.

Certain amino acids like glutamic acid, asparagine and aspartate can be oxidized to pyruvate, producing alanine or to alpha-ketoglutarate, producing glutamine. The others must first be deaminated before they can be utilized. In the muscle, deamination is accomplished by transamination from branched-chain amino acids. In the liver amino acids are deaminated by urea production which is excreted in the urine. After severe trauma or sepsis as much as 20 g/day of urea nitrogen is excreted in the urine. Since 1 g urea nitrogen is derived from 6.25 g degraded amino acids, this protein wastage amount to 125 g/day. One gram muscle protein represents 5 g wet muscle mass. Such a patient would be losing 625 g of muscle mass per day. A loss of 40% of body protein is usually fatal because failing immunocompetence leads to overwhelming infection.

The intestinal mucosa has a rapid synthesis of amino acids. Depletion of amino acids results in atrophy of the mucosa causing failure of the mucosal antibacterial barrier. This may lead to bacterial translocation from the gut to the portal system and is probably one of the causes of liver injury, overwhelming infection and multisystem failure after severe trauma.

The Anabolic Phase

During this phase the patient is in positive nitrogen balance, regains his weight and restores his fat deposits. The hormones which contribute to anabolism are growth hormones, androgens and 17-ketosteroids.

Clinical and Therapeutic Relevance

Survival after injury depends on a balance between the extent of cellular damage, the efficacy of the metabolic response and the effectiveness of treatment. Hypovolaemia due to both external losses and internal shifts of extracellular fluid seems to be the major initiating trigger for the metabolic sequence. Fear and pain, tissue injury, hypoxia and toxins from invasive infection add to the initiating factor of hypovolaemia. The degree to which the body is able to compensate for injury is astonishing, although sometimes the compensatory mechanisms may work to the patient's disadvantage. *Adequate resuscitation to shut off the hypovolaemic stimulus is important. Once hormonal changes have been initiated, the effects of the hormones will not cease merely because hormonal secretion has been turned off by replacement of blood volume.* Thus once the metabolic effects of injury have begun, therapeutic or endogenous restitution of blood volume may lessen the severity of the metabolic consequences but cannot prevent them.

To measure the rates of transfer and utilization of amino acids mobilized from muscle or infused into the circulation, the measurement of central plasma clearance rate of amino acids (CPCR-AA) has been developed. Using this method a large increase in peripheral production and central uptake of amino acids into the liver has been demonstrated in injured patients, especially if sepsis is also present. The protein-depleted patient can be improved ... present. Amino acid infusions in patients who ultimately die, cause plasma amino acid concentration to rise to high levels with only a modest increase in CPCR-AA. This may be due to hepatic dysfunction caused by anoxia or toxins liberated by bacteria responsible for sepsis. Possibly inhibitors, which limit response to IL-1 and PIF, may be another explanation.

Mobilization and storage of the energy fuel substrates, carbohydrates, fats and protein is regulated by insulin balanced against catecholamines, cortisol and glucagon. However, infusion of hormones have failed to cause more than a modest response.

Therapy should be aimed at removal of the factors triggering the response. Thorough resuscitation, elevation of pain, surgical debridement and where necessary drainage of abscesses and appropriate antibiotic administration coupled with respiratory and nutritional supporft to aid defense mechanisms are of fundamental importance.

Chapter 3.2: Acid-Base Metabolism

J. P. Pretorius

Introduction

The acidity of body fluids is a dynamic variable, impinged upon continuously by a wide variety of competing forces. Hydrogen ions are the toxic end-product of metabolism and affect physiologic and biochemical cellular phenomena. The ideal intracellular pH is near neutrality so that the ionization essential to intermediary metabolism of the cell can occur. At pH levels above 7.60 or below 7.10 dysfunction of vital organs results. To prevent this dysfunction, the acidic products of metabolism must be neutralized or buffered or excreted. The body maintains the hydrogen ion concentration of the extracellular fluid within a remarkably narrow range despite large fluctuations in dietary intake and a host of stresses

imposed by daily activity and disease. Maintaining a normal pH requires the integration of a number of physiologic mechanisms, which include cellular and extracellular buffering, and the compensatory action of the lungs and kidneys. It is important to note the physiological context within which the following dissociation-recombination reaction occurs.

water + CO_2 <==> carbonic acid <==> H+ + bicarbonate

The carbonic acid-bicarbonate buffer pair is the dominant buffer in acid-base regulation.

Chemical Considerations

Definitions

An acid is a substance that dissociates into component ions and, in so doing, donates a proton or hydrogen ion to the solution:

Acid <==> H+ + Base-.

A base is a proton or hydrogen ion acceptor. The electrical charge of a substance is not related to its acid-base qualities, i.e. an acid can be:

Neutral: CH_3COOH <==> CH_3COO^- + H^+

Positively charged: NH_4^+ <==> NH_3 + H^+

Negatively charged: $H_2PO_4^-$ <==> HPO_4^{--} + H^+

Both organic and inorganic acid-base pairs are commonly encountered in biological systems.

carbonic acid/bicarbonate
monobasic/dibasic phosphate
ammonium/ammonia
acetic acid/acetate

Maany protein molecules also contain acidic groups that may dissociate. The cycle of dissociation and subsequent recombination is a never-ending process of an individual acid molecule. When the rates of these opposing reactions counterbalance each other exactly, a state of equilibrium exists. The *mass action expression* states that at chemical equilibrium, the ratio of the concentration products of the opposing reaction sets is a constant:

K = (H+ x Base) / Acid

(or rearranged to highlight the property of acidity)

H+ = K x (Acid/Base)

K is termed the *dissociation constant,* and is a measure of the strength of a given acid. The strength of an acid is determined by the degree to which it dissociates. Strong acids dissociate freely, or more or less totally, and have high K values (i.e. HCl or H_2SO_4). Weak acids dissociate sparingly and have low K values (i.e. CH_3COOH or H_2CO_3).

Dissociation-recombination occurs whenever an acid-base substance is placed in solution. In an aqueous solution, water is a crucial participant, because water itself can also dissociate slightly:

$$\mathbf{H_2O <==> H+ + OH-}$$

By convention the concentration of the hydrogen ion in pure water serves as a neutral reference point: 7 (on a scale ranging from 0 to 14). In complex solutions containing multiple acid-base solutes, the concentration of hydrogen ions at equilibrium is determined by the composite influence of the hydrogen ion affinities of each of the individual molecular products present, in conjunction with their relative concentrations:

$$\mathbf{H+ = K_1 \ x \ (Acid_1/Base_1) = K_2 \ x \ (Acid_2/Base_2)}$$

Buffer Action

Any change in the acidity of such a complex solution thus involves a redistribution of H+ ions among all of the acid pairs present. Addition of an acid or base will result in a smaller change in hydrogen ion concentration than addition of the same acid or base to pure water. This ability of solutions containing acid-base pairs to resist change in acidity is termed *buffering,* and the acid-base pairs are termed *buffers.* The extent to which such buffering takes place is determined by:

- the initial hydrogen ion concentration

- the dissociation constants, pK

- the respective concentrations of the individual buffer pairs present.

The best buffers are weak monobasic acids with their strong conjugate bases. A well-mixed, homogeneous solution can have only one hydrogen ion concentration = the *isohydric principle.* Knowledge of the dissociation constant and the component concentrations of a single buffer pair is sufficient to monitor the acid-base behaviour of any homogeneous system, no matter how complex. This principle simplifies the analysis of acid-base changes in living organisms because it permits us to concentrate on the physiologically pre-eminent buffer pair, carbonic acid-bicarbonate:

$$\mathbf{PaCO_2 ==> CO_2 \ diss + H_2O =carbonic \ anhydrase=> carbonic \ acid ==> H+ + HCO_3}$$

Acidity is measured in terms of the pH unit, which is defined as the negative logarithm of the hydrogen ion concentration:

$$\mathbf{pH = - \ logH+ = K(Acid/Base)}$$

Remembering previous equations it follows that:

pH = pK + log(Base/Acid)

This is called the *Henderson-Hasselbach equation.*

pH = pK + log(bicarbonate/carbonic acid)
= pK + log(bicarbonate/0.03 x $PaCO_2$)
= 6.1 + log(24/0.03 x 40)
= 6.1 + log(20/1)
= 6.1 + 1.3
= 7.4

Remembering that the log of 1 = 0, the above equation defines the px of a weak acid as *that pH at which the acid is 50% dissociated,* i.e. with equal quantities of acid (HA) and base (A+). In a solution of pH one unit larger than the pK, the ratio of base to acid will be 10:1, and at pH two units larger than pK, the ratio will be 100:1. Thus, over a pH range of two units above and below its pK, a weak acid is titrated from being present essentially totally dissociated (basic form), to being present essentially totally undissociated (acidic form). For this reason the maximum range over which a weak acid can function as a buffer is ± two pH units on either side of its pK. Effective body buffers are limited then to those available weak acids which have a pK within two pH units of 7.4.

They are:

- carbonic acid/bicarbonate

- haemoglobin/haemoglobinate

- protein/proteinate

- monobasic phosphate/dibasic phosphate

Patients with anaemia, low plasma-protein levels, or decreased muscle mass have reduced buffering capacity, and are apt to have wide swings in pH when they become ill or injured. In such patients impaired tissue perfusion of relatively short duration may cause a severe acidosis. Most of the body's buffer systems are set up primarily to neutralize acid. As a consequence the body generally handles an acid load better than it handles a base excess.

Physiologic Considerations

Maintenance of Homeostasis

To maintain acid-base balance the body, in addition to promptly buffering acid and base loads, can employ specific respiratory mechanisms to compensate for an acid-base abnormality. Rapid-acting respiratory and slower-acting renal compensatory mechanisms together with the primary acid-base disorder therefore determine the final blood pH. Nevertheless, it is very important to realize that no compensating organ ever overcompensates

for a primary acid-base abnormality, for the simple reason that the stimulus for compensation will diminish as the pH approaches normal. These concepts are very important, especially in critically ill patients with compromised or failing organs which might not be able to fulfil their compensating roles.

Sudden, usually iatrogenic, correction of the primary acid-base disorder may lead to the appearance of a different acid-base abnormality because of the compensatory process. This should be kept in mind when instituting therapy - advanced and chronic acid-base disorders should not be altered rapidly and without regard for the pH, which should be monitored closely.

The Carbon Dioxide System

Carbon dioxide, CO_2, the major end-product of cellulat metabolism, is continuously produced by all tissues from aerobic metabolism of carbohydrates and fats, at a rate of about 200 mL/min or 12-20,000 mmol/day. When compared to the 250 mL/min of oxygen consumed, the ratio of the two is referred to as the metabolic respiratory quotient, with a value of 0.8. Although changes in physical activity, diet, fever, drugs, etc, may alter daily CO_2 production, primary change in volatile acid synthesis has not been recognized as a cause of respiratory acid-base disorders. Movement of CO_2 across membranes occurs (like O_2) by passive diffusion. CO_2 is about 20 times more soluble than O_2 and it immediately saturates the extracellular fluid to a concentration dependent upon the $PaCO_2$. As shown in fig. 3.2.1, carbon dioxide is transported from the peripheral tissue cells to the lungs:

- In plasma as:

- physically dissolved CO_2
- bicarbonate ion
- carbamino compounds with plasma proteins
- carbonic acid

- In red blood cells:

- dissolved CO_2
- bicarbonate ion
- carbamino-haemoglobin

CO_2 exists in the body in an "open system", in which CO_2 enters continuously from metabolizing cells, and leaves continuously via the lungs. Because the atmospheric air one inspires has only 0.03% CO_2 a gradient or driving pressure (measured as $PaCO_2$) develops from the cells via the plasma, and from plasma to expired air. The net result is to wash out continuously any CO_2 entering this open system. The $PvCO_2$, which represents the pooled CO_2 output from all tissues is 46 ± 4 mm Hg. The $PACO_2$ is 40 mm Hg, and determines $PaCO_2$. Thus, $PaCO_2$ is $\pm$ 22 mm Hg at sea level (normal range 35-48 mm Hg). Most of the carbon dioxide transported in the blood is carried by the buffering system of the red blood cells (> 65-90%). The amount remaining in plasma is small (< 5-30%) but is the only factor that determines the CO_2 pressure gradient or $PaCO_2$ (fig. 3.2.1).

Carbonic anhydrase catalyzes the hydration of CO_2 to carbonic acid in red blood cells and renal tubular cells. It does not appear free in plasma and therefore hydration of CO_2 in plasma takes place slowly. The largest fraction of intraerythrocyte CO_2 is hydrated to form carbonic acid, which immediately dissociates into H+ and bicarbonate. The H+ is buffered by haemoglobin which is a more potent buffer in the relative hypoxaemia of venous blood. Bicarbonate diffuses into the plasma in exchange for Cl- and this chloride shift maintains electroneutrality across the red blood cell membrane. Another fraction of intraerythrocyte CO_2 combines directly with nitrogen groups on haemoglobin to form carbamino-compounds, just as dissolved CO_2 in plasma may combine with amino-groups on plasma proteins. CO_2 has a reciprocal relationship with O_2. A decreased PCO_2 aids in the unloading of oxygen at tissue level. The enhancement of CO_2-transport by haemoglobin as it loses O_2 is known as the Haldane effect. Thus, haemoglobin buffering, bicarbonate and carbamino formation greatly expand the CO_2-carrying capacity of blood beyond that available to dissolved CO_2 alone.

When venous blood with its high $PvCO_2$ and high total CO_2 reaches the alveolus, the entire sequence is reversed: venous blood CO_2 diffuses down its chemical gradient into the lung. As $PvCO_2$ falls, haemoglobin releases H+, converting bicarbonate back to CO_2. Cl- shifts back to plasma, and CO_2 is reformed from carbamino compounds. In normal man, CO_2 excretion varies directly with both PCO_2 and the rate of alveolar ventilation.

CO_2 excretion = $PACO_2$ x alveolar ventilation.

Owing to the diffusibility of CO_2, $PACO_2$ are are virtually identical. In the steady state, the CO_2 excretion rate is equivalent to the CO_2 production rate, thus:

$PaCO_2$ = CO_2 production / alveolar ventilation

Carbonic Acid-Bicarbonate Buffer System

This buffer pair is not only the dominant buffer in extracellular fluid, but even more importantly, it is the only buffer whose component concentrations can be varied independently by physiological regulatory systems. Changes in plasma acidity, whether they be physiological adjustments or pathophysiological disturbances, can be mediated only through changes in $PaCO_2$ and/or bicarbonate. As these two variables can change independently, this buffer pair functions as the crucial link between the chemical process of buffering on the one hand, and the physiological process of acidity regulation on the other. The lungs control the level of carbonic acid in the extracellular fluid by setting the $PaCO_2$ between narrow limits: 35-40 mm Hg at sea level. $PaCO_2$ therefore, gives an indication of the respiratory acid-base status. Without alteration of pulmonary ventilation carbonic acid neither rises nor falls.

Bicarbonate serves as a major anionic constituent of the extracellular compartment and is maintained at relatively high concentration by the kidneys (450 mmol of bicarbonate stroed in the body is about 1000 mmol - for the most part as sodium bicarbonate). Intracellular bicarbonate concentration is probably 12-16 mmol/L, in arterial blood the concentration is 24 mmol/L and in venous blood 25 mmol/L. In physiological ranges of $PaCO_2$ (± 40 mm Hg) a 1 mm Hg change in $PaCO_2$ will alter bicarbonate by only 0.2 mmol/L. Because of the high plasma concentration of bicarbonate, dissociation of carbonic acid must proceed in the face of a large quantity of its conjugate base. The likelihood of recombination is therefore greatly

enhanced and equilibration is reached at a concentration of H+ ions that is correspondingly very low, or in other words, the reaction will tend to move to the left. Using equations given previously the mass action expression can be written as:

H+ = K x (carbonic acid/bicarbonate)

Acidity of body fluids can be expressed either in pH units or as the hydrogen ion concentration in nanomoles/L (= 1 x 10^{-9} moles/L). Remembering that CO_2 dissoled == bicarbonate == $PaCO_2$ and using the constants appropriate for plasma, it follows that under normal conditions:

H+ = 24 x ($PaCO_2$/Bicarbonate) = 24 x (40/24) = 40 mmol/L (or pH 7.40)

This equation enables the clinician to verify the bloodgas analysis. Substituting the actual values of the measured variables into this equation, will allow one to check the accuracy of the measurements. If equality cannot be proven, there is an error in one of the components of the equation. This is possible because at a pH of 7.40, every increase or decrease of 0.01 pH units, will change H+ approximately 1 nanomol in the opposite direction.

The following arterial bloogas analysis provides an example:

pH : 7.31
$PaCO_2$: 37 mm Hg
bicarbonate : 18 mmol/L

The decrease of 0.09 pH units should cause an increase of 9 nanomol in the H+, or pH 7.31 should reflect a H+ of 40 + 9 = 49 nanomol/L. Substituting the measured values for $PaCO_2$ and bicarbonate into an equation should also yield a value of 49:

24 x ($PaCO_2$/Bicarboante) = 24 x (37/18) = 49.3

This bloodgas determination is acceptable.

CO_2 - content

CO_2- content refers to the total of all the carbon dioxide present in the blood, normally 24-31 mmol/L. In the plasma, this includes carbonic acid, bicarbonate, and the carbamino compounds. Under ordinary circumstances plasma bicarbonate is approximately 1.0-2.0 mmol/L less than the CO_2-content.

Buffer Base

In patients with a mixed acid-base disturbance (i.e. respiratory alkalosis with metabolic acidosis) it is occasionally difficult to determine whether the alteration in bicarbonate concentration is due to an abnormality in metabolizing renal cell function or compensatory change. The concept of whole-blood buffer base as the sum of buffer anions is an attempt to differentiate which of these changes are primary and which secondary. Normal: 45-55 mmol/L.

Elevated buffer base: base excess associated with metabolic alkalosis.

Lowered buffer base: base deficit associated with metabolic acidosis.

Standard Bicarbonate

The standard bicarbonate concepts represents the amount of bicarbonate that would be present if the $PaCO_2$ were normal, i.e. 40 mm Hg. Abnormal bicarbonate with $PaCO_2$ = 40 mm Hg cannot be due to an attempt of the body to compensate for a respiratory abnormality, but rather due to primary metabolic acidosis or alkalosis. Actual bicarbonate refers to the bicarbonate actually in the patient's blood, whatever the $PaCO_2$ present.

Base Excess

The base-excess concept specifies the number of millimoles of acid or base needed to titrate one litre of blood to pH 7.40 at 37 °C, while $PaCO_2$ is constant at 40 mm Hg. As an index of deviation from the normal base concentration, the base excess is expressed in millimoles per litre above or below the normal buffer-base range. Thus normal value: 0 ± 2 mmol/L. Base excess may suggest a greater metabolic disturbance than is indicated by a change in bicarbonate alone. Base excess is changed only by nonvolatile acids and thus measures the true non-respiratory acid-base status. The numerical magnitude of the base deficit provides a therapeutic guideline for sodium bicarbonate administration according to: Base needed (mmol) = 0.3 x base excess x body weight in kg. In practice, usually one half of the calculated amount is given initially. Base excess is then reevaluated and recalculated. It is important to realize that in this way, only blood base excess, and not total body base excess is treated. Likewise base excess deficit is not simply the difference between the normal and the patient's bicarbonate level. In acid-base disorders, especially metabolic disorders, intracellular pH is still a major problem because we are unable to measure it. A specific measured change in extracellular pH does not necessarily reflect the extent of intracellular pH alteration. In metabolic acidosis, following circulatory shock, for instance, the cells generate the lactic acid themselves and are relatively acidic before there is a change in extracellular pH. A thorough understanding of the patient's total clinical situation is always essential.

Hydrogen Ion Input and Body Buffering

Acids are only rarely present as such in the diet. Waste products of metabolism are mostly acidic substances that can release hydrogen ions. Incomplete breakdown of fats, proteins and neutral carbohydrates forms organic acids. Some organic acids are true end-products of metabolism, i.e. uric acid and creatinine. Oxidation of cystine and methionine forms sulphuric acid, and hydrolysis of phosphoesters forms phosphoric acid. Other organic acids are metabolic intermediates and contribute to the acid load only when generated faster than they can be converted to water and CO_2, i.e. aceto-acetic acid, beta-hydrohy-butyric acid and lactic acid. Under normal dietary conditions endogenous acid production is approximately 1 mmol/kg/day in adults (or 50-70 mmol/day) and 2-3 mmol/kg/day in infants. Aerobic metabolism of glucose and fat produces approximately 12000-20000 mmol/day of hydrogen ions through the conversion of CO_2 to carbonic acid and the dissociation of this acid.

When an acid produces a gas in this manner, and the gas can be eliminated, the acid

is said to be volatile. This volatile acid is dealt with by the lungs. The much smaller amount of acid which cannot be converted to a gas is called non-volatile or fixed, and is dealt with by the kidneys. Nevertheless, the kidneys excrete much greater amounts of H+, but these H+ are mostly a byproduct of Na+ and bicarbonate reclamation and neogenesis. A wide variety of metabolic and respiratory factors could cause a wide swing in the blood pH if it were not for the buffering system of the body. This is collectively termed body buffering. These chemical buffers respond together almost instantaneously to the addition of strong acids or bases to the system (mainly bicarbonate). Secondarily, modulation by the lungs occurs relatively rapidly (in minutes). Over longer period (days) the kidneys start to play a role. Approximately 50% of the daily endogenous H+ load is buffered with bicarbonate.

To prevent tissue damage H+ is immediately taken up by cell buffers, mainly protein. The K+ released from the buffers associate with the acid anions (sulfate, phosphate) to form potassium salts. Because of the pressure of continuous new formation of H+, these are passed on from buffer to buffer - first within the cells and later in the extracellular fluid. As the potassium buffer salts leave the cells, the K+ are replaced by the Na+ so that the phosphate buffer pair in the intracellular fluid is phosphate. Eventually, the H+ ions reach the carbonic acid/bicarbonate buffer pair, where they displace Na+ to form carbonic acid. As there is no immediate change in the $PaCO_2$, no increase carbonic acid can occur, and newly formed carbonic acid must of necessity break down into CO_2 and water.

The net effect on body fluid composition is thus a depletion of bicarbonate stores and conversion of some nonbicarbonate buffer bases to their respective acid forms. It should be apparent that body buffering, despite its critical role in blunting the immediate impact of acid loads, makes no direct contribution toward external H+ balance. Body buffering merely substitutes one change in body composition, namely, conversion of certain bases to their acid forms, for another much less desirable change, namely, a marked increase in H+. Until body composition is restored by replacing the deficit of available base, positive H+ balance and a tendency for acidification of body fluids will persist.

Pulmonary Regulation of Acid-Base Balance

In the normal human, as governed by the relationship of $PaCO_2$, bicarbonate and carbonic acid in previously given equations, an acute alteration in $PaCO_2$ of 10 mm Hg will result in a change of 0.08 pH units. A readily available evaluation of CO_2 excretion would provide a quantitative assessment of the pulmonary cotribution to acid-base regulation. Measurement of the $PaCO_2$ is the most direct and most useful indication of adequacy of alveolar ventilation and the contribution of the pulmonary system to acid-base regulation. Basically three factors affect $PACO_2$ and thus also $PaCO_2$:

- Blood-to-atmosphere CO_2-gradient.

- Potential diffusion barriers to CO_2 transfer.

- Effectiveness of pulmonary ventilation.

Measurements used to evaluate the status of ventilation are:

- Effective ventilation which is equivalent to alveolar ventilation and represents the amount of exchanged gas that is in contact with functioning gas exchanging units of the lung.

- Dead space ventilation which is that fraction of pulmonary gas exchange that does not reach normally functioning alveolar spaces:

1. Anatomic dead space (no gas exchange).

2. Alveolar dead space (alveoli not being perfused).

- 3. Ventilation-perfusion inequality (ventilation in excess of perfusion).

Larger tidal volumes (800-1000 mL/breath) and slower rates (10-12 breaths/min) are the most effective ventilatory patterns for carbon dioxide removal, because they provide less dead space and more efficient ventilation. Chemoreactors in the brainstem adjust ventilatory efficiency (by changing rate and depth of breathing) in response to the slightest changes in $PaCO_2$. This regulation is probably not directly mediated by carbon dioxide, but rather through the hydrogen ion content of cerebrospinal fluid (pH-CSF). Schematically, this may be expressed as:

Elevated $PaCO_2$ ==> lowered pH ==> elevated cerebral interstitial H+ ==> respiratory centre stimulation ==> hyperventilation ==> lowered $PaCO_2$ ==> lowered carbonic acid ==> elevated pH of extracellular fluid

Likewise,

elevated pH ==> depresses respiratory centre ==> decreases alveolar ventilation ==> elevated $PACO_2$ ==> elevated carbonic acid ==> lowered pH.

It is uncommon for $PaCO_2$ to increase by any other mechanism. This negative feedback control mechanism is extremely efficient. Plasma bicarbonate affects the control of ventilation by mechanisms that are not yet well understood. Loss of bicarbonate activates hyperventilation in an attempt to remove hydrogen ions via CO_2 excretion (i.e. diabetic ketoacidosis). Hyperventilation causes acute impairment of renal H+ excretion and bicarbonate reabsorption.

Renal Regulation of Acid-Base Balance

The pulmonary and renal regulatory processes are integrally interrelated via the Henderson-Hasselbach equation. In this context this equation can be written as:

$pH = bicarbonate/PaCO_2$ = Kidney function/Lung function

The overall process of extracellular fluid bicarbonate buffering of acids would deplete the body stores of bicarbonate unless the buffering action was reserved and bicarbonate were to be replenished somehow.

This does occur in the kidney provided that the urine formed is more acidic (pH 4.0)

than the blood (pH 7.4). When fixed acids are excreted intact because they cannot be fully ionized at the pH value of plasma or urine, a second mechanism operates. Naturally, when bicarbonate is regenerated, serum bicarbonate reserves will be replenished. During an acid load the kidney returns more bicarbonate to the body fluids than it receives in the glomerular filtrate by maintaining a rate of Na+/H+ exchange to below the bicarbonate filtration rate.

The 50-100 mmol fixed acid excreted daily to balance endogenous acid production represents less than 2% of the H+ actually secreted by the kidney. At normal filtration rate of 180 L/day, a normal plasma bicarbonate of 24 mmol/L the daily H+ secretion rate required to prevent excretion of filtered bicarbonate is more or less 4500 mmol. The secretion of acid by the kidneys results in a urine H+ of at most 3×10^{-5} moles/L, with a resultant minimum pH of about 4.5. Endogenous acids burden the extracellular fluid not only with H+ but with an equivalent number of relatively non-reabsorbable anions (sulfate, phosphate, and various organic anions). The kidney excretes H+ by generating "new" H+ within its cells to combine with phosphates and other components in the urine. The major acids in the urine include phosphoric acid, creatinine, and beta-hydroxybutyric acid. In regulating acid-base balance, the major function of the kidney, in addition to excreting fixed acids and a small percentage of the total H+ loss, is to retain bicarbonate in the blood. This is accomplished by three major pathways (fig. 3.2.2). The first pathway involves formation of carbonic acid. CO_2 dissolved in the extracellular fluid diffuses into the renal tubular cells. Carbonic anhydrase in these cells hydrates CO_2 to carbonic acid which ionizes to H+ and bicarbonate. The H+ passes into the filtrate in exchange for Na+ from a molecule of sodium bicarbonate. The bicarbonate remaining in the filtrate associates with the H+ to form carbonic acid. The Na+ which returns to the cell associates with the bicarbonate in the cell to form sodium bicarbonate, which diffuses into the extracellular fluid. This is sodium bicarbonate neogenesis (regeneration). The carbonic acid which has been formed in the glomerulat filtrate is split into water and CO_2 by carbonic anhydrase on the outside of the tubular cells. The CO_2 diffuses back into the cells and is immediately converted to carbonic acid by carbonic anhydrase.

The carbonic acid dissociates and the H+ ions are again exchanged for Na+ which, together with the bicarbonate, returns to the extracellular fluid. This is termed reclamation of sodium bicarbonate. H+ can only leave the cell if replaced by Na+, and bicarbonate can only return to the extracellular fluid if accompanied by Na+. Under normal circumstances all the sodium bicarbonate is reclaimed from the glomerular filtrate. When this supply of Na+ for exchange is exhausted, the Na+ required for further neogenesis is obtainable from sodium diphosphate, which is reduced to sodium monophosphate as in fig. 3.2.2C.

If the demand for sodium bicarbonate neogenesis still continues, the kidney has a final mechanism for retrieving Na+ from the filtrate without producing phosphoric or hydrochloric acid. Tubular cells are able to deaminate glutamine to glutamate and ammonia. The ammonia diffuses into the filtrate to join the H+ excreted from the cells to form ammonium which accompanies phosphate or chloride, releasing Na+ to return to the cells.

Several factors other than ednogenous acid production are known to influence the bicarbonate reabsorption and acid excretion by the kidneys. Chronic hypercapnia for instance accelerates H+ secretion, producing a sustained elevation in plasma bicarbonate. Chronic hypocapnia leads to dampening of H+ secretion and reduced plasma bicarbonate. Expansion of the /// causes a dilutional hypervolaemic acidosis and serves as a stimulus for bicarbonate

conservation by the kidney. The reverse can occur, cauing a contraction hypovolaemic alkalosis. However, volume expansion or contraction *per se* does not influence acid-base equilibrium when the process responsible for the volume alteration does not alter the concentration of plasma electrolytes. Lastly, recent evidence indicates that the K+ deficit in metabolic alkalosis is a consequence of the alkalosis and not its cause. Contrary to general opinion, hypokalaemia *per se*, in the absence of volume depletion, does not generate metabolic alkalosis. In fact, isolated hypokalaemia, which directly inhibits aldosterone secretion, actually leads to metabolic acidosis. However, when plasma K+ is high, acid secretion is depressed in the kidneys, the urine become alkaline, and a low plasma bicarbonate develops, resulting in hyperkalaemic acidosis. When plasma K+ is low, bicarbonate is high, and hypokalaemic alkalosis develops as H+ increases in the cells, because no K+ is available to drive it out. The result is a paradoxical aciduria in the presence of hypokalaemic alkalosis.

Approach to Acid-Base Problems

Definitions

- **Acidaemia/Alkalaemia:** the suffix "-aemia" describes blood acidity or pH.

- **Acidosis/Alkalosis:** the suffix "-osis" refers only to primary metabolic or respiratory processes generating H+ or OH- without regard to blood acidity.

- **Compensation:** primary metabolic disorders evoke offsetting, or compensatory respiratory changes, and vice versa.

- **Acidity:** the resulting balance between $PaCO_2$ and HCO_3- defines final blood acidity (equation J).

In a patient with a single acid-base disorder, acidosis usually will lead to acidaemia. The problem arises when two or more acid-base disorders present simultaneously - in such a case acidosis may be present without acidaemia.

Categorizing the Abnormality (fig. 3.2.3)

Simple acid-base disturbances imply, primary respiratory acidosis or alkalosis, and likewise primary metabolic acidosis or alkalosis with the relevant compensatory mechanisms. Mixed acid-base disorders denote the simultaneous coexistence of two or more simple disorders in the same patient at the same time. Correct analysis of mixed disorders is of considerable diagnostic and therapeutic value.

Limits of Compensation

When evaluation acid-base disturbance it is useful to remember that lack of appropriate compensation for a simple disturbance provides evidence for a mixed disturbance. One must also bear in mind that compensation rarely corrects the pH to normal except in chronic respiratory alkalosis. Certainly, compensation never overcorrects.

Clinical Approach to Diagnosis of Acid-Base Disturbances

The following strategy ensures a logical approach to the problem:

- Suspect the disturbance from the history.

- Suspect the disturbance from the physical examination.

- Evaluate laboratory data:

- HCO_3-: if raised, think of metabolic alkalosis or compensated respiratory acidosis.

- HCO_3-: if lowered, think of metabolic acidosis or compensated respiratory alkalosis.

- K+: if raised, think of acidaemia.

- K+: if lowered, think of alkalaemia.

- Cl-: if raised, think of hyperchloraemic metabolic acidosis.

- Cl-: if lowered, think of metabolic alkalosis.

- Anion gap.

- Evaluate blood gas values.

Common Clinical Acid-Base Problems

Acid-base metabolism is frequently disturbed during surgical practice - especially major surgery, particularly in the elderly and the very young. The presence of infection, shock, intestinal obstruction or fistulae predispose patients to acid-base disturbances. Patients with cardiorespiratory or renal failure are also at risk. It may be difficult to identify the essential cause of an acid-base fault and full history-taking, clinical evaluation, and biochemical investigation may be necessary. In patients with multiple organ failure, mixed acid-base disorders present the clinician with a great challenge in which the stakes may be the life or death of the patient.

Simple Acid-Base Disturbances

Metabolic Disorders

There are limits to the extent that the body can tolerate changes in PCO_2 and compensation fails when the bicarbonate concentration continues to change after these limits have been reached.

Metabolic Acidosis

Pathophysiology

Disruption of the normal interplay between production, buffering and excretion of acid causes accumulation of fixed acid and hypo-bicarbonataemia - the hallmarks of metabolic acidosis. Overproduction of acid due to increased synthesis, as in lactic acidosis or ketoacidosis, may overwhelm the homeostatic mechanisms and result in bicarbonate consumption. On the other hand, loss of buffer stores due to intestinal or renal bicarbonate wasting may have the same end point. Underexcretion of acid, as may happen in chronic renal failure, is another cause of metabolic acidosis. The kidneys are unable to excrete the normal daily acid load. Consequently serum bicarbonate falls and is replaced by various other anions. Basically the decreased serum bicarbonate raises the $PaCO_2$/bicarbonate ratio and this explains the decrease in equation J. Acidification of extracellular fluid stimulates the respiratory centre causing hyperventilation hypocapnia as a result. This respiratory compensating mechanism tends towards normal. Adding 15 to the measured serum bicarbonate should yield the last two digits of the pH, i.e. chronically acidotic patients with serum bicarbonate = 10 mmol/L, will have a pH of 7.25.

Electrolyte Patterns

The interplay of accumulating protons and anions with normal serum components results in electrolyte patterns that allow for classification of all types of metabolic acidosis. Since lost alkali is replaced by acid anions (phosphate, chloride, acetoacetate and proteins) it follows that any acid other than HCl, replaces the easily measured bicarbonate anion with anions that are not routinely measured. The anion gap reflects the balance between the routinely measured major cation Na+ and the routinely measured anions Cl- and bicarbonate.

$$\mathbf{AG = Na^+ - (Cl^- + HCO_3^-)}$$

Hyperchloraemic or normal anion gap acidosis reflects an equal exchange of lost bicarbonate for retained chloride, without altering serum Na+. The anionic gap remains within normal range: 12 +/- 2 mmol/L. All other forms of metabolic acidosis increase the anion gap by replacing bicarbonate with anions other than chloride. An anion gap greater than 30 mmol/L virtually always indicates the presence of metabolic acidosis, usually lactic or keto-acidosis. Acidosis has the following biological effects:

- Epinephrine release is stimulated

- Leukocytosis of 30-60.000/mm^3 may develop

- Hyperkalaemia commonly occurs

- Enhanced mobilization of calcium from bone

- Emesis is stimulated

- Life-threatening haemodynamic alterations namely impaired myocardial contraction,

direct myoinhibitory effect of acid as pH falls below 7.20 or myocardial failure and pulmonary oedema may result.

The differential diagnosis is summarized in table 3.2.1.

Table 3.2.1. The differential diagnosis of metabolic acidosis

Elevated anion gap	Normal anion gap
Renal failure	Hypokalaemic acidosis
Ketoacidosis	Renal tubular acidosis
Starvation	Diarrhoea
Diabetes mellitus	Loss of duodenal,
Alcohol associated	pancreatic, biliary fluids
	Post-hypocapnic acidosis
Lactic acidosis	Carbonic anhydrase inhibit:
	Acetazolamide, mafenamide,
Clinically apparent tissue hypoxia	Ureteral diversions:
Severe anaemia	Uretero-sigmoidostomy,
Haemorrhage/hypotension	ileal bladder
Shock states	Normal-hyperkalaemic
Congestive heart failure	acidosis
Severe hypoxia	Early renal failure
	Hydronephrosis
Clinically inapparent tissue hypoxia	Additional HCl, NH_4, NH_4Cl
Common disorders: Uraemia, tumours	Sulphur toxicity
Liver failure, seizures	Hypoaldosteronism
Drugs: biguanides, ethanol, methanol, fructose	
Hereditary & acquired metabolic defects	
Toxins	
Methanol	
Ethylene glycol	
Salicylates	
Paraldehyde	

Treatment

The treatment of metabolic acidosis in the first inctance, is to find and correct the primary problem, i.e. for shock this includes improvement of tissue perfusion and correction or removal of the cause of shock. For diabetes mellitus, administration of intravenous fluids and insulin is essential to correct the acidotic state.

Normal Anion Gap Acidosis

Gastrointestinal secretions from the duodenum onwards contains bicarbonate which may be lost by aspiration, fistula or diarrhoea. In the presence of ileus, the loss of bicarbonate is always greater than observed, because of the sequestration of intraluminal content. The

electrolyte content of intestinal fluid may vary. The principle of replacement is to administer a close approximation to the requirement, and to check the adequacy of therapy by daily electrolyte measurements on plasma and urine.

Pancreatic and biliary losses should be replaced volume for volume by a solution containing more or less 25 mmol/L bicarbgonate or equivalent, in addition to normal plasma concentrations of Na+ and Cl-. Ringer's lactate solution meets these requirements. Potassium supplements should be given according to serum K+.

Increased Anion Gap Acidosis

In the metabolic acidosis that exists during exertion or hypoxia, lactate is the predominant unmeasured anion. Mild lactic acidosis is compensated for by the respiratory system. Sodium bicarbonate, administered intravenously has never been rigorously tested for treatment of this disorder, and increasing evidence suggests that it may actually worsen the prognosis of patients with lactic acidosis.

Lactic acidosis is not merely an epiphenomenon in the unrelenting course of a dying patient. Its own intrinsic morbidity must be treated vigorously. Because there is no safe and effective specific therapy available, the only course lies in early recognition and treatment of the underlying disease. It is becoming more and more evident that intravenous administration of sodium bicarbonate, often in massive amounts, which has become an accepted part of conventional resuscitative measures, lacks benefit and this intervention presents potential hazards in critically ill patients who have ketoacidosis or who are in the acute stages of cardiopulmonary arrest.

Replenishment of bicarbonate lost during active acidosis takes place through either metabolic oxidation of organic anions effecting resynthesis of bicarbonate, or renal bicarbonate synthesis.

However the alkali used for acute parenteral therapy is sodium bicarbonate. Avoid solutions containing calcium. Sodium lactate or acetate are effective substitutes but must first be oxidized to bicarbonate - this could be a disadvantage in hypotensive patients or those with advanced liver disease.

Indications for administration of alkali are the level of the pH and rate of acid production. At pH 7.20 acidaemia's haemodynamic consequences begin to appear. Bicarbonate therapy is therefore usually considered when pH falls below this level.

Blood pH and bicarbonate must be repeatedly checked during therapy which takes the form of a "titration experiment", until the desired therapeutic effect is achieved. Complications of sodium bicarbonate therapy (1 mL 8.5% sodium bicarbonate contains 1 mmol of bicarbonate) are:

- Hypernatraemia with a hyperosmolar state

- Volume overload (i.e. acidotic renal failure patient)

- Potential fall in intracellular pH

- Hypokalaemia with cardiac and peripheral myscle dysfunction

- Potentially arrhythmogenic shifts in intracellular and extracellular electrolytes

- Overshoot alkalosis

- Increased affinity of haemoglobin for oxygen

- Tissue hypoxia

Metabolic Alkalosis

Pathophysiology

Sustained hyperbicarbonataemia is the primary event. This may result from the loss of protons or the gain of exogenous base. The coupling of increased bicarbonate production with its renal retention ensures maintenance of hyperbicarbonataemia. The kidney cannot excrete the excess bicarbonate while the stimulus for increased proximal renal tubular reabsorption of bicarbonate continues to be present. This may be volume depletion, hypokalaemia, hypoparathyroidism or a high PCO_2 level. Respiratory compensation through alkalinization of brainstem chemoreceptors, depresses alveolar ventilation causing mild hypoxia, and a degree of hypercapnia. The increased $PaCO_2$ represents the respiratory compensation that returns the $PaCO_2$/bicarbonate ratio of the pH and H+ toward normal. As $PaCO_2$ rises because of hypoventilation, or slow shallow breathing, the $PaCO_2$ falls. Because the chemoreceptors will not allow it to fall much below 60 mm Hg, hypoxia imposes a definite limit on the amount of respiratory compensation possible. The alkalotic patient may also be at risk from spontaneous arrhythmia at times of stress, i.e. surgery and anaesthesia. Other metabolic effects are:

- Increased affinity of haemoglobin for oxygen

- Mild increase in the anionic gap

- Enhanced glycolysis and tendency toward hyperglycaemia

- Enhanced renal reabsorption of calcium

- Decreased net renal reabsorption of potassium

Severe metabolic alkalosis reduces the amount of ionized calcium present in the plasma, thereby increasing the neuromuscular irritability and impairing cardiovascular function. Hypokalaemia that often develops secondary to the alkalosis may also interfere with muscle function.

The causes of metabolic alkalosis include:

- Excessive removal or vomiting of gastric acid (most common cause)

- Hypokalaemia (due to diuresis or diarrhoea)

- Steroid administration (causing Na+ and bicarbonate retention and K+ excretion). Primary hyperaldosteronism, Cushing's syndrome, and other causes of mineralocorticoid excess are all associated with enhanced renal H+ losses.

- Massive transfusions (with citrate combination with hydrogen)

- Administration of large quantities of Ringer's lactate

- Administration of antacids

- Sepsis

- Dehydration

The diagnosis depends on a base excess or a bicarbonate level exceeding 26 mmol/L. Often an associated hypokalaemia and hypochloraemia also exist. In patients with metabolic alkalosis the reduced $PaCO_2$ due to compensatory hypoventilation may result in an erroneous diagnosis of pulmonary insufficiency.

Differential Diagnosis

Most patients with metabolic alkalosis require the accompaniment of extracellular fluid volume contraction to stimulate renal bicarbonate reabsorption thereby preventing bicarbonaturia from dissipating the elevated serum level. Reduction in the extracellular fluid volume will cause alkalosis only if there is loss of iso-osmotic NaCl and water. These alkaloses are therefore reversible with saline-induced re-expansion of the extracellular fluid. Renal Na+, Cl- and bicarbonate retention and K+ wasting characterize these disorders and the urinary concentration of these electrolytes reflect this:

Na+ and Cl- usually 10 mmol/L
pH 7.0
K+ usually 15-20 mmol/L

These saline responsive alkaloses are best sub-classified as to the source of elevated extracellular fluid bicarbonate, i.e. contraction, renal or gastrointestinal or derived exogenously. Saline unresponsive alkalosis is derived from renal synthesis, and in some cases from hypocalcaemia and hypoparathyroidism that cause enhanced reabsorption of bicarbonate in proximal renal tubular cells. These disorders are characterized by urine Na+ and Cl- concentrations that exceed 15-20 mmol/L. The presence of hypertension is another differential point that allows for a clinically useful subclassification as, for example, in primary hyperaldosteronism and Cushing's syndrome.

Treatment

Metabolic alkalosis can be divided into two broad groups, as far as treatment is concerned but first, one must attempt to identify and correct the cause of the event initiating the alkalosis. It is therefore necessary to decide whether the patient has lost acid, gained base or suffered acute volume contraction with iso-osmotic NaCl loss.

Saline-Responsive Alkalosis

Hypotensive patients with poor tissue perfusion should be repleted more aggressively than those manifesting with only mild postural hypotension. The former needs parenteral therapy whereas the latter can be treated with oral salt and potassium. In a recent article Rosen et al reported that chloride repletion in the form of oral potassium chloride idependent of sodium repletion, or change in volume status, or increased glomerular filtration rate, corrected the metabolic alkalosis in patients with a negative sodium balance and reduced plasma volume. They also found that sodium repletion without chloride repletion, did not. Urinary bicarbonate excretion increased during correction. In addition, they found that administration of an identical potassium chloride load to similar sodium - depleted but not chloride - depleted normal subjects produced no change in acid-base status. They conclude that chloride repletion *per se* can correct saline-responsive metabolic alkalosis by a renal mechanism without restoring plasma volume. Thus, the hypothesis that chloride depletion *per se* can maintain alkalosis, is applicable to humans with saline (or chloride) responsive alkalosis (i.e. secondary to vomiting, diuretics or after recovery from hypercapnic acidosis).

This article proves the existence of a specific bicarbonate-chloride exchange or linked proton and chloride secretion in the kidney independent of sodium, and it disproves the classical explanation that saline-responsive metabolic alkalosis is dependent on volume contraction *per se*. But, it goes without saying that, if the pathophysiology of the underlying disease includes volume depletion, the patient should still be treated accordingly and not only the metabolic alkalosis. Saline therefore, is still the appropriate basic therapy for patients with metabolic alkalosis due to profuse vomiting etc. Potassium deficits may reach 500 mmol. Ongoing K+ losses must also be replaced. Although exceptions do occur, it is best to avoid giving more than 10 mmol/hour. Remember that changes in serum K+ are opposite to those of pH. For every 0.1 increase in pH, serum potassium levels tend to decrease by 0.5 mmol/L. Persisting gastric losses may be controlled by administering 200 mg of Cimetidine every 6 hours. Alkalotic but edematous patients with normal renal function should be treated with diamox (bicarbonaturetic diuretic) 125-500 mg IV once daily together with K+ replacement. Acidifying agents are rarely indicated. Renal failure patients manifesting with marked neuromuscular excitability, cardiotoxicity and pH in excess of 7.5-7.55 should receive acid therapy, as should patients with hepatic failure. Systemic acidification is safely and efficiently achieved with parenteral HCl, given via a large central vein as a 0.2 M solution at a rate of 15-20 mmol/hour. In practice one hundred millilitres of 2 M hydrochloric acid may be added to one litre of 5% dextrose in a glass bottle (200 mmol of HCl per litre or 0.2 mmol per one millilitre). This solution may be infused through a central venous catheter only, at a rate of no greater than 0.2 mmol/kg/h. For example: to lower the serum bicarbonate by 15 mmol/L in a 70 kg man with a serum bicarbonate of 40 mmol/L and an extracellular volume of 14 L a total of 210 mmol of HCl should be given over 12-24 hours monitored by repeated acid-base measurements. As soon as the arterial pH reaches 7.36 or less, the hydrochloric acid

infusion should be discontinued.

Saline-Unresponsive Alkaloses

Severe potassium depletion (in excess of 500-1000 mmol) can cause chloriuresis and alkalosis. Aggressive parenteral therapy is required. Mineralocorticoid excess is best treated with 300-600 mg daily of aldactone (spironolactone). Triamterene 200-300 mg daily is also useful and is effective within hours as opposed to the days required by aldactone. Surgical correction of adrenal tumours should, of course, be carried out in appropriate circumstances. These patients generally are not hypovolaemic.

Respiratory Acid-Base Disorders

Respiratory Acidosis

Pathophysiology

Simple respiratory acidosis is characterised by increased $PaCO_2$ (> 45 mm Hg), which elevates the $PaCO_2$/bicarbonate ratio and thereby causing the H+ to rise. As a general rule, an acute rise in $PaCO_2$ will cause serum bicarbonate to increase by 1 mmol/L for each 10 mm Hg rise in $PaCO_2$. The progressive hyperbicarbonataemia which occurs in chronic hypercapnia is quantitatively more important. This is the direct result of increased acid excretion (mostly as NH_4) and consequent HCO_3- synthesis by the kidneys. In the chronic case serum bicarbonate will increase by 3.5 mmol/L for each 10 mm Hg increase in $PaCO_2$. In planning therapy for patients with respiratory acidosis, the distinction between acute and chronic forms of the disorder is critical.

Clinical and Laboratory Manifestations

Alteration in the state of consciousness varying from confusion to stupor, to frank coma can be seen. This, together with manifestations of increased intracranial pressure, may be due to the cerebral vasodilatory effect of increased $PaCO_2$. As the serum bicarbonate rises, there is a progressive fall in serum chloride. Remember, the electrolyte pattern in chronic respiratory acidosis resembles that in metabolic alkalosis: hyperbicarbonataemia and hypochloraemia.

Treatment

The principle once again is to correct the cause, restore alveolar ventilation and correct as much of the CO_2 retention as possible. Sodium bicarbonate has no major role to play here. Endotracheal intubation and assisted ventilation is necessary in patients with a progressive increase in $PaCO_2$ or central venous system manifestations or hypercapnia. To improve alveolar ventilation, bronchodilators such as aminophylline or sympathomimetic agents such as isoproterenol or adrenalin may be administered. It is essential to proceed slowly when correcting severe, chronic respiratory acidosis. Too rapid correction after a compensatory metabolic alkalosis has developed, can cause a sudden severe combined metabolic and respiratory alkalosis and can result in severe arrhythmias, seizures, or death. Therefore $PaCO_2$ should not be corrected faster than 2-5 mm Hg/hour. In patients with acute trauma or hypoxic

damage to the brain, correction or prevention of acute respiratory acidosis may be very important. Hypercapnia can greatly aggravate cerebral oedema, due to vasodilation. Ventilatory maintenance of a mild to moderate respiratory alkalosis ($PaCO_2$ 25-300 mm Hg) may induce sufficient vasoconstriction to reduce cerebral oedema. Management of chronic CO_2 retention in patients with severe chronic obstructive pulmonary disease requires a more conservative approach: bronchodilators and chest physiotherapy are the mainstay, while antibiotic therapy is important when infections are diagnosed. These patients tolerate CO_2 retention rather well, acidaemia is usually not severe, and hypercapnia no longer effectively stimulates respiration. Controlled O_2 therapy (to prevent atrophy of the hypoxic drive) and all reasonable conservative measures should be administered before resorting to intubation and ventilation.

Respiratory Alkalosis

Pathophysiology

Inappropriate hyperventilation causes hypocapnia, a 10 mm Hg decrease in the $PaCO_2$ causes an increase in the pH of approximately 0.08. Patients suffering from shock, sepsis, or trauma who are not hyperventilating have an increased chance of developing respiratory failure. When $PaCO_2$ declines acutely, the pH rises because H+ is titrated by bicarbonate to form water and cabon dioxide. The extent of the increase in extracellular pH is slightly reduced because bicarbonate moves intracellularly in exchange for chloride. Intracellular pH rises also because of low intracellular PCO_2, and stimulates glycolysis which increases lactic acid production. Protons derived by this mechanism further titrate extracellular bicarbonate to bring the pH to normal. Sustained hypocapnia lowers bicarbonate by 5 mmol/L for each 10 mm Hg fall in $PaCO_2$ through renal retention of endogenously produced acid, coupled with mild bicarbonaturia. This compensatory renal mechanism takes longer than the cell buffering response, often two or three days. The only acid-base disturbance where the compensatory response can restore the pH to normal is chronic respiratory alkalosis.

Clinical and Laboratory Manifestations

Circumoral and digital paraesthesias and carpopedal spasms mimic hypocalcaemia or hypermagnesaemic tetany. Central nervous system effects, such as light-headedness, nausea and vomiting are not uncommon. The laboratory manifestations include hypobicarbonataemia, hyperchloraemia, hypokalaemia and hypophosphataemia, and a small increment in the anion gap. This electrolyte pattern is also seen in certain forms of metabolic acidosis. The serum potassium concentration is often used to differentiate acidotic and alkalotic processes, since its serum concentration is often increased by the former and decreased by the latter.

Treatment

In asymptomatic patients with a pH of more or less 7.55, treatment should be aimed at the primary cause and not the pH. Only symptomatic patients require attention to their alkalaemia.

- Use a simple rebreathing device like a paper bag in order to increase the concentration of inspired CO_2 until the $PaCO_2$ rises to about 30 mm Hhg.

- In emergencies where the alkalaemia is associated with life-threatening cardiac arrhythmias and altered mental status, extreme measures may be considered.

- Acetazolamide (diamox) - a carbonic anhydrase inhibitor, induces bicarbonate diuresis - this becomes less effective as serum bicarbonate falls.

- IV hydrochloric acid.

- Critically ill patients with mild to moderate respiratory alkalosis who are not on a ventilator may be sedated cautiously.

- Controlled ventilation as last resort in the most acutely ill. The pH and $PaCO_2$ must be closely monitored. Fortunately, in most instances, respiratory alkalosis requires no therapy, and serves only as a clue that an underlying disease process is present, manifesting itself with inappropriate hyperventilation.

- Patients on a ventilator can also be sedated and dead space can be added gradually between the patient and ventilator to increase the $PaCO_2$ to 35 mm Hg.

Table 3.2.2. Causes of respiratory acidosis

a. Central depression of respiration

1. Drug overdose (narcotics, barbiturates)
2. Central nervous system trauma or tumour
3. Infections of the nervous system
4. Cerebrovascular accidents
5. Primary central hypoventilation

b. Primary pulmonary disease

1. Chronic obstructive lung disease
2. Severe status asthmaticus
3. Severe pulmonary infections
4. Adult respiratory distress syndrome
5. Chest wall disease
6. Neurological disorders affecting muscles of respiration
7. Sleep disorders

Table 3.2.3. Causes of respiratory alkalosis

a. Central mechanisms

1. Anxiety
2. Metabolic encephalopathy
3. CNS infestion
4. Cerebrovascular accidents
5. Hypoxaemia

6. Gram-negative septicaemia
7. Salicylate intoxication
8. Pregnancy

b. Pulmonary mechanisms

1. Pneumonia
2. Asthma
3. Pulmonary emboli
4. Early interstitial lung disease
5. Congestive heart failure

Mixed Acid-Base Disturbances

Clinical Approach

Taking a careful history might reveal major causes for the simple acid-base disorders that should be kept in mind. Paid-base disorders common in certain clinical settings should also be remembered. Ingestion of certain drugs should be noted. Look for signs and symptoms during physical examination, i.e. extracellular fluid volume contraction, tetany, cyanosis, fever. Examining the serum electrolytes and biochemistry might also provide clues about the underlying disease, i.e. elevated serum creatinine, renal failure and metabolic acidosis. Increased serum glucose with positive serum ketones found in diabetic ketoacidosis presents another example. Serum HCO_3-, K+ and Cl- again may provide useful information. Remember to calculate the anionic gap: AG = Na+ - (Cl- + HCO_3-) ranging from 8-16 mmol/L. Measurement of pH and $PaCO_2$ is also necessary to document a mixed disturbance and to determine the extent of acidaemia or alkalaemia upon which the need for treatment should be based.

Analysis of the blood gas indices should begin with a check to see if the values are consistent with the Henderson-Hasselbach equation. Then examine the pH, $PaCO_2$ and HCO_3- to determine if the values are indicative of a simple or mixed disturbance. Therefore, when the $PaCO_2$ is above or below the predicted value for compensation of a metabolic disturbance, or when the HCO_3- level is above or below the level expected for compensation of a given respiratory disorder, a mixed disturbance is present. It should be remembered that in simple disturbance, $PaCO_2$ and HCO_3- are always deviated in the same direction. Therefore, if the $PaCO_2$ and HCO_3- are altered in opposite direction, a mixed disturbance must be present.

Important Causes of Mixed Acid-Base Disturbances, and their Treatment

When making therapeutic decisions about mixed acid-base disturbances, two principles must be borne in mind:

- The aim of treatment is to return blood pH to normal. Therefore, pH must be monitored to determine when to begin or discontinue therapy.

- The effrect of treatment of one disturbance on the manifestation of the second disorder should be anticipated.

Examples of Mixed Axid-Base Disturbances

- **Respiratory acidosis with metabolic acidosis:** This combination is found with cardiopulmonary arrest, severe pulmonary oedema, or drug ingestion with central nervous system depression. In these cases the serum bicarbonate is usually low, the $PaCO_2$ normal or elevated, and the pH may be dangerously low. CO_2 retention prevents respiratory compensation for the metabolic acidosis and the metabolic process prevents compensation for the respiratory acidosis. Improvement of ventilation as well as bicarbonate therapy is urgent. Hyperkalaemia is frequently a serious problem, and measures to displace it intracellularly or to remove it from the body are necessary.

- **Respiratory alkalosis and metabolic alkalosis.** This combination may be the consequence of hepatic failure and diuretics. Patients receiving mechanical ventilation and nasogastric suction are also at risk. Serum bicarbonate is usually elevated, the $PaCO_2$ is normal or low and the pH is alkaline. The profound alkalaemia which may result demands immediate specific therapy. As compensation is poor, in order to return the pH toward normal, treatment should again be aimed at correcting metabolic alkalosis. With the patient receiving ventilatory assistance, settings should be readjusted to increase the $PaCO_2$. Spontaneous hyperventilation is difficutl to treat unless the underlying process can be corrected.

- **Respiratory alkalosis with metabolic acidosis** may be expected in conditions such as septic shock, renal failure with sepsis, salicylate overdose, or pulmonary embolism. In this case the anion gap may be increased, the serum bicarbonate is usually very low, and $PaCO_2$ independently depressed beyond the limits of respiratory compensation of a metabolic acidosis. The pH may be normal or just mildly deviated from normal. Treatment should be aimed at correcting the underlying processes. Examining the respiratory compensation for the metabolic acidosis is critical, since the respiratory alkalosis will be missed until it is recognized that ventilation is greater than predicted by compensatory responses alone. Bicarbonate therapy may be contraindicated.

- **Respiratory acidosis with metabolic alkalosis** should be recognized in patients suffering from chronic lung disease and CO_2 retention, or diuretics. The $PaCO_2$ is elevated, the serum bicarbonate is elevated more than expected, and the pH may be normal or mildly depressed. Treatment should be aimed at correcting the pH. The primary metabolic alkalosis should be treated with volume, Cl- and K+ replacement, since the elevated bicarbonate may itself depress respiration further. This is very important when trying to wean a patient with chronic CO_2 retention from the respirator.

- **Mixed acute and chronic respiratory acidosis:** Chronic lung disease with superimposed infection in the respiratory tract is the cause of this malady. Retained CO_2 produces a renal response with resulting elevation of serum bicarbonate. Superimposed acute impairment of respiratory function leads to further CO_2 retention.

In this case the history is of prime importance. The $PaCO_2$ of +/- 75 mm Hg, which is higher than would be tolerated on a chronic basis, therefore implies acute change, while the bicarbonate of 33 represents evidence of chronically elevated $PaCO_2$. Treatment should be directed at improving ventilatory function to lower $PaCO_2$ and ventilatory support will

usually be necessary until the infection or other events can be reversed.

- **Metabolic alkalosis with metabolic acidosis** may be found in patients suffering from renal failure and vomiting, or vomiting and hypotension, or volume depletion and lactic acidosis. $PaCO_2$ and bicarbonate may be high, low or normal, and pH is often close to normal. An increased anionic gap may be the clue to the presence of metabolic acidosis. Treatment is again aimed at the underlying processes, but it must be remembered that resolution of one disturbance will permit the second abnormality to emerge unopposed.

Comment

Acid Base

J. W. Mostert

Life can be defined as an unceasing struggle against the hydrogen ion. It is evident, however, that it is still a source of perplexity to many clinicians. As stated by Pretorius, the classic Bronsted-Lowry nomenclature defines an acid as a hydrogen ion donor and a base as a H+ acceptor, whereas Gamble of Harvard University designated cations such as sodium and potassium as bases, and chloride and bicarbonate as acids, not bases!

The body produces two major types of acid, carbonic acid and nonvolatile acids. The former is excreted by the lungs as CO_2, the latter are excreted by the kidneys.

The body also produces base; the Singer and Hasting's "buffer base" (BB) of about 47.5 mmol/L consists of the most important bicarbonate, normally 24 mmol/L, haemoglobin 6.5 mmol/L, and protein 17 mmol/L. The interrelationship between CO_2 and bicarbonate is the major determinant of acid base status. Henderson expressed it as: $H+ = K \times H_2CO_3/HCO_3-$.

However, the concept that considers normal acid or base content to be zero, and which refers to an excess or deficit as delta PCO_2 (acid) and delta base, respectively has been basic during five decades of debate. Thus, the acid factor directly gives the CO_2 tension in terms of excess or deficit, which in turn gives an accurate measure for treating hypoventilation or hyperventilation.

The delta base, or base factor, should also be regarded in terms of mmol/L deviation from normal! (+ 25 mEq/L to - 35 mEq/L)

One has to understand that buffer base will vary with oxygenation because oxygenated haemoglobin is more acid than reduced haemoglobin. Therefore venous blood has a slightly higher BB value than arterial blood. In addition, BB also varies with pH and PCO_2, and therefore BB is sensitive to respiration.

If, instead of using BB, we use the CHANGE in BB from normal at pH 7.40 and PCO_2 40 mm Hg, we then eliminate the effect of pH and PCO_2. Astrup and Siggaard-Andersen called this factor "base excess" (BE) = BB minus normal BB.

But "base excess" is an awkward expression because we sometimes must speak of a "negative base excess" to describe a deficit of base. When reported simply as "delta base" (or change in base) the base factor (B) of blood equalts the plus or minus deviation of base from normal. This is not affected by respiration, and really is the non-respiratory (metabolic) factor.

A New Acid-Base Ratio

Gambino of Columbia University, New York, first noted that when A/B ratio reduces to the simple fraction 2/1, the pH is always normal. For example, if the deviation on the **respiration A scale** in the figure is numerically twice that on **Metabolism B scale,** the unbroken horizontal lines will always exhibit the normal pH of 7.4. Tipping (angling) of the broken line denotes an imbalance by the altered pH value, in this case a shift downward into the very acid of 6.95. This *staircase approach* to the acid-base imbalance must be clearest and most helpful of all the numerous slide rules and elaborate graphs for depicting the progress of acid-base balance as a yard-stick of improvement, especially after treatment of the underlying vital processes rather than symptomatic correction of the indirect acid-base pointers to bodily disturbances.

Identical values were obtained from a patient in haemorrhagic shock whose delta PCO_2 was minus 20 because of hyperventilation, but the delta base of minus 30 identified the dominant factor of excess lactic acidosis. The most urgent need was clearly correction of the delta base component with, firstly, whole blood transfusion and then only if restoration of the vital signs had not spontaneously restored the normal 2:1 ratio, should bicarbonate administration be considered. The underlying cause of the acidosis must always be dealt with before recourse to alkaline therapy.

A simple way of demonstrating clinical acid-base aberration is to measure the arterial pH (pHa), then blow through the blood specimen to produce froth with one's own alveolar expiratory air which should have a PCO_2 of 40 mm Hg. The new pH is then measured (pHe or eucapnic pH). Medical students are usually fascinated to find that the two measurements of the pH are identical. One, the arterial pH is a measure of acid-base compensation in the patient. The other, at out own PCO_2 of 40 mm Hg is a quantitative measure of nonrespiratory changes, the metabolic change in BB, base excess, base deficit or whatever you want to call it. The relationship between the two values is an excellent measure of the original PCO_2 in the patient. If the arterial pH was higher then we clearly must have blown some CO_2 out of the specimen by blowing into it.

It has been repeatedly suggested that a better understanding of the quantities involved would be to express acidity directly in equivalents per litre of hydrogen ions, and because of its high dilution, the term nanoequivalents (neq = 10 exp -9) was suggested. This is said to be in line with other biological standards and it has the advantage of a linear relationship with whole numbers. The relationship between H+ expressed as 'microequivalents' and 'nanoequivalents' on one hand, and pH on the other, are given here with the figures between the dotted lines expressing the normal physiological limits:

Table 3.2.4

pH (-log H+)	micro equivalent	nanoequivalent
7.9	0.012	12
7.70	0.020	20
7.42	0.038	38
7.40	0.040	40
7.10	0.080	80
6.90	0.126	126

Pretorius alludes to the manner of drug-ionization. An example helps to elucidate this effect of acid base variation. pH of phenobarbitone is 7.2 and antilog of 0.3 = 2. Thus, at H+ of 64 nanomoles/1 the pH = 7.2, pK = 7.2, and log 1/1 means that the ratio of ionized to non-ionized drug will be 50/50 in brain and blood and 25/50 at a pH of 7.2 and urine at a pH of 6.9.

As Gamble described and Pretorius discussed in great detail, the acid-base balance focuses on the volume, composition, and position of plasma to determine if a body fluid disturbance is present. Since cations must always equal anions, if the bicarbonate becomes elevated, the chloride must be depressed, if the bicarbonate goes down, the chloride must rise. While such changes result from "chemical compensation", they in themselves give rise to important physiological disturbanes: alkalosis, if the bicarbonate rises to much; acidosis, if it is depressed excessively. But there are other anions of great significance besides bicarbonate and chloride; organic acids, i.e. lactic acid and the ketone bodies such as acetoacetic acid, normally occur in ECF in the amount of 5 or 6 mEq/L. They are called "unidentified" or "unmeasured" anions because we do not ordinarily identify them separately. Should their levels rise above 14-16 mEq/L, we know we have an abnormal acid production in the body. These organic acids, if present in excess, neutralize bicarbonate so that bicarbonate deficit, or metabolic acidosis results.

The unidentified anions have been lumped together under the special name of **delta.** No assessment of a patient with a body fluid disturbance is complete without measurement of delta. Usually delta does not appear, as such, on laboratory reports, but we can calculate it quickly: add the chloride and the bicarbonate, and subtract the sum from the total Na. Suppose we have following values: Cl=103mEq/L; HCO_3=26mEq/L, and Na=142mEq/L. Using the formula 142 - (103 + 26) = 13 mEq/L.

Finally, a new perspective of hyponatraemia as a complication of perioperative fluid therapy must be noted. Practically a whole issue of the New England Journal of Medicine was devoted to the report of Allen Arieff under the title "Hyponatraemia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women". Nausea, emesis, and headaches occurred in all patients, with psychiatric symptoms, in half including hostility, confusion, depression, and hallucinations. All patients suffered *grand mal* seizures. The average intake was 8.8 litres of 285 mM glucose containing less than 5 mmole of sodium chloride per litre. The net fluid balance waqs + 7.5 litres. The average serum sodium (68 +/- 10 mmoles/L) and urinary osmolarity (501 +/- 53 mOsm/kg) in the presence of water intoxication and hyponatraemia are virtually diagnosti of the syndrome of inappropriate

antidiuretic hormone secretion. Although 7 of the 14 patients recovered from coma after the serum sodium was increased to 131 mmoles/L, coma recurred within 2-6 days. Final outcomes included death in 27 percent of patients, limb paralysis in 13 percent, and a persistent vegetative state in 60 percent. In the editorial in the same journal Naims noted that we do not know if the complications were caused by the severity of the hyponatraemia, or the speed of its correction, which was 0.7 mmoles/L. A panel of experts polled by Naims recommended that an increase to 2 mmoles/L per hour as 5 percent saline is the optimal mode of treatment. Nowever, only prospective studies which had not been done at this time will determine whether this widely held view is correct. This syndrome is similar to the TURP (transurethral prostatectomy) syndrome due to absorbed irrigation fluid. The following equation allows estimation of the volume of irrigation solution thathas been absorbed: Volume absorbed = preoperative serum Na/serum Na/postoperative serum Na x ECF - ECF. The serum sodium level is determined in out theatres by flame photometry, and the extracellular fluid (ECF) is estimated from body weight (20-30% of body weight in kg).

When the Na level falls below 120 mEq/L hypotension occurs; below 115 mEq/L bradycardia and widening of the EKG QRS complex occurs; below 100 mEq/L seizures, respiratory and cardiac arrest have been reported.

Nothing else devastates the acid-base balance so readily as hypoxia. In the young adult at sea-level the arterial oxygen tension is 13 kPa, bu tonly 11 kPa on the highveld and lowveld of Transvaal. If the patient is over 65 years, mthe normal value, while breathing ambient air, is only 9 kPa. Deviation from these values are the crucial players in the ensemble of acid-base disturbances.

Chapter 3.3: Cardiovascular Dysfunction

J. P. Pretorius, J. C. W. Badenhorst

Part I

Recognition and Management of Cardiac Failure

Introduction

It is obvious that the heart cannot be studied in isolation - it forms the centre of the circulation. Traditionally, cardiac performance has been described solely in terms of the pumping capabilities of its ventricles. This view, which emerged from the laboratories of Frank and Starling, has emphasized the relationship between the diastolic volume of the ventricles and their stroke volume.

Blood flow to each organ system is determined by the mean arterial pressure generated by the heart and by the resistance to blood flow imposed by that organ system, through autoregulatory mechanisms. The rate of pumping (cardiac output) is usually diminished in heart failure, but it may be normal or even elevated when peripheral demands are great. Thus, the precise level of cardiac output is less important than its relationship to peripheral needs.

One must remember that it is less important which drug or drugs are chosen to treat a patient, than to understand the mechanism, the advantages and liabilities of the drug you choose and to carefully monitor its effect and be able to alter or combine pharmacology when ongoing monitoring suggests continued haemodynamic insufficiency.

The development of congestive heart failure (CHF) is significant because it carries a mortality of 0.15-60% depending on the underlying disease. Approximately 200.000 patients per year die from CHF in the USA. It is the most common medical discharge diagnosis for patients over 65 years of age. The prevalence of CHF in the USA is between 2 and 3 million patients. Approximately 400.000 patients per year develop CHF, and as the population becomes more aged, this incidence will increase since the incidence of CHF is twice as great in the seventh decade of life than the fourth. At every age more males than females have CHF presumably because of the greater incidence of ischaemic heart disease in males. The natural history of patients with CHF shows a five-year survival rate of 50%.

Definitions and Physiological Concepts of Cardiac Function

The cardiovascular system is the transport system through which life and function of the cells are maintained. To produce flow (Q), blood is subjected to a force or pressure (P) generated by the heart. Translation of this pressure wave into flow is impeded by the frictional resistance of the blood vessels, the inertia of blood, and the elastic properties of the vessel walls. In the peripheral systemic circulation the most important component of this impedance is resistance (R) so that Q = P/R. This simplified equation illustrates the interrelationship of flow, pressure and resistance.

It is important to realize that although hypotension is one of the commonest clinical problems in critically ill patients, the adequacy of blood flow or tissue perfusion is more important. The function of the system is to deliver flow, but the normal physiological monitoring of central haemodynamics is based largely upon pressure. Although the presence of pressure does not guarantee flow, the monitoring of systemic pressure has proved to be a very reliable index of the adequacy of the circulation.

Constant flow necessary to meet fluctuating energy requirements in various organs, can be maintained over a wide range of pressures through a process called **autoregulation.** This local control mechanism is largely dependent on the influence of the local concentration of metabolites upon regional arteriolar and precapillary sphincter tone.

Whenever any element of this control is missing, compensatory reflexes try to maintain central blood pressure regardless of autoregulation. The pressure head is monitored by baroreceptors and after integration in the brainstem, pump function as well as systemic vascular resistance is modified by increased sympathetic discharge. In the peripheral circulation alpha receptors cause vasoconstriction and beta receptors vasodilatation. The degree to which local autoregulation is overruled thus depends upon the balance of adrenoreceptors. In this way blood flow to vital organs such as the brain and myocardium is maintained at the expense of less important tissues such as gut and skin. Renal blood flow also drops dramatically during acute hypotensive episodes to reduce urine output and preserve intravascular volume.

The term heart (or cardiac) failure implies that cardiac performance is inadequate to pump blood at a rate required for the body's metabolic demands. This may frequently be due to a defect in myocardial contraction, i.e. in myocardial failure. In other patients no abnormality of myocardial function is present and heart failure is caused either by an excessive load or ventricular filling is impaired. Circulatory failure, on the other hand, entails an abnormality of some component of the circulation - heart, blood volume or vascular bed, which is responsible for inadequate cardiac output. It is important to realize that myocardial failure, heart failure and circulatory failure are not synonymous, but refer to progressively broader entities. Sufficiently severe myocardial failure will always cause heart failure. A number of conditions which can suddenly overload the heart (i.e. acute infective endocarditis with acute aortic regurgitation) will produce heart failure in the presence of normal myocardial function. Heart failure will always produce circulatory failure but not conversely. Any low output state (i.e. hypovolaemic shock) can produce circulatory failure while cardiac function is normal.

The heart can compensate for defective myocardial contraction or excessive haemodynamic burden by three principal compensatory mechanisms:

- **The Starling mechanism** - an increased preload (i.e. lengthening of sarcomeres to provide optimal overlap between thick and thin myofilaments acts to sustain cardiac performance within physiologic limits. This is also termed the preload reserve.

- **Increased release of catecholamines** by adrenergic cardiac nerves and the adrenal medulla, which increases myocardial contractility.

- **Myocardial hypertrophy** - with or without cardiac dilatation, in which the mass of contractile tissue is increased.

Starling's "Law of the Heart"

Original Definition

"Within physiological limits, the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at each contraction". (Starling, 1915)

Implication

Within limits, the degree of initial muscle stretch is related to the intensity of muscle contraction.

Working Definition

Increasing end-diastolic pressure (preload) increases stroke work to a maximum value.

Limitations of Concept

- In many important clinical situations ventricular compliance, and hence the relation between end-diastolic voume and pressure is not constant.

- At a fixed end-diastolic volume, stroke volume changes with afterload.

- The curve is undefinable for an end-diastolic volume greater than that associated with maximum work, and the heart should never operate in that region. Injury results, and the heart will move to a different operating curve.

- A change in cardiac output may be caused by moving on the curve or moving to a different curve.

Clinical Utility

To optimize pumping performance, and efficiency, for a given contractility, filling pressure should be adjusted to just below that for maximum stroke work. Filling pressure must never be increased to where the slope is almost zero (see fig. 4).

Although these three mechanisms may initially be able to maintain the heart's pumping performance, each has a limited potential and ultimately fails. The clinical syndrome of heart failure occurs as a result of the limitations and/or the ultimate failure of these compensatory mechanisms.

It is clear that heart failure may manifest in several ways. In some cases the emphasis falls on the left ventricle and in others on the right ventricle, and the terms left and right heart failure are used. When both ventricles fail, the term biventricular failure is used.

Although cardiac function may deteriorate from many causes, it is necessary to determine the levels of dysfunction. With impaired contractility but stroke volume effectively adjusted to normal, the ventricle is termed dysfunctional. When the adaptive responses are overwhelmed and stroke volume falls, the ventricle has failed - this usually occurs as a chronic progressive deterioration in function. At the other end of the spectrum are the acute syndromes of acute circulatory failure (cardiogenic shock) and acute circulatory congestion (pulmonary edema).

Congestive cardiac failure is the most prevalent form of chronic heart failure and it usually is a mixture of three separate components:

- impaired contractile behaviour with decreased force development and shortening of contractile elements

- a decreased inotropic state, where greater filling pressure is associated with the same stroke volume, so that pulmonary congestion and increased venous pressure develop (circulatory congestion or backward failure). There is also a decreased cardiac output which impairs peripheral perfusion and causes muscle fatigue (circulatory insufficiency or forward failure).

- neurohumoral changes in the periphery: increased sympathetic tone, activation of the renin-angiotensin system and fluid retention with peripheral congestion and oedema.

Previously it was speculated whether forward or backward failure was the major problem, but it is difficult to see how one could occur without the other, since the cardiovascular system is a relatively closed loop. Functionally, the cardiovascular and pulmonary systems form an integrated unit - the cardiopulmonary system.

It is important to realize that the physiology of the heart includes not only a study of the function of the normal organ, but also a study of its cellular organization and contractile activity. Knowledge of myocardial cellular metabolismj is essential to an understanding of the physiological function of the contraction cycle of the heart, and to the mode of action of modern therapeutic agents such as beta-adrenergic blockers, calcium-channel antagonists and load-reducing agents.

Aetiology

The left and the right heart chambers do not function independently of each other, but rather maintain a very fine balance between their output and synchronization.

Pathophysiologically heart failure can be classified as follows (table 3.3.3).

Table 3.3.2. Causes of congestive heart failure

1. Excessive pressure load

    - Aortic stenosis
    - Arterial hypertension
    - Pulmonary stenosis
    - Pulmonary hypertension

2. Excessive volume load

    - Aortic or mitral regurgitation
    - Pulmonary or tricuspid regurgitation
    - High-output states

3. Loss of heart muscle tissue

    - Myocardial infarction

4. Decreased contractility

    - Cardiomyopathy
    - Myocarditis
    - Metabolic heart disease
    - Endocrine heart disease

5. Impaired LV filling

- Cardiac tamponmade
- Constrictive pericarditis
- Endomyocardial fibrosis
- Restrictive cardiomyopathy
- Tigh mitral stenosis

- Excessive pressure load

This can affect either the left ventricle or the right ventricle trough an afterload effect.

- Excessive volume load

This again can affect both the ventricles, due to valvular lesions such as aortic, pulmonary or tricuspid incompetence or due to high output states such as arteriovenous fistulae, thyrotoxicosis, anaemia, and Paget's disease. One must also remember that both tricuspid as well as mitral incompetence can be the result of a dilated heart affecting the mitral or tricuspid ring. In such a case the valvular incompetence will be the result rather than the causative factor.

- Loss of heart muscle tissue

This commonly occurs in patients with myocardial infarction. Patients with repeated myocardial infarction will have progressively less muscle tissue left and heart failure may ensue. If more than 40% of the LV myocardium are damaged suddenly, acute pulmonary oedema and cardiogenic shock will develop.

- Decreased contractility

The mechanical demand on the myocardium exceeds the supply of contractile work, or the amount of myocardial tissue available for contractile purposes, is reduced.

It is useful to bear in mind that contractile failure may be global or segmental. Global decrease of contractility may be the result of the cardiomyopathies, hearts overloaded by either hypertension or valvular abnormalities as well as critical illness with shock or multiple injury. Segmental ventricular dysfunction is most commonly associated with ischaemic heart disease.

- Impaired LV filling

Although the cause is not really left or right ventricular failure, the condition leads to the clinical picture of heart failure.

Usually there is a single or dominant cause but it is possible that more than one will be present later in the course of the disease. Consequently a patient with chronic rheumatic endocarditis and mitral incompetence may later develop cardiomyopathy as well. In the same way any patient with existing heart failure may also develop ischaemic heart disease, which

will then be contributory to the heart failure, independent of the primary condition.

Pathophysiology

As mentioned before, depending on the underlying cause of failure, the heart will respond to failure in one of the following ways:

- **The Starling mechanism** - an increased preload increases the end-diastolic volume and pressure which stretches the end-diastolic fibre length and increases the stroke volume. In this regard one must remember that in the normal myocardium, distention by a volume load leads to increased pressure. If the pressure-volume relationship is normal, the compliance (an index of stiffness) is normal. If there is fibrosis or myocardial infarction, compliance is lost - in technical terms, the modulus of elasticity is increased. The decreased compliance leads to a decreased distention of the myocardium so that an increase of volume greatly increases intraluminal pressure. The result is that the wall tension rises more than expected and the oxygen demand increases correspondingly; the demand outstrips the supply. Loss of compliance is therefore one factor leading to deterioration of the situation of the heart on the Frank Starling curve.

- **Myocardial hypertrophy,** i.e. an increase in the muscle mass or the quantity of heart muscle tissue.

- **Increased catecholamine secretion** due to neural and humoral stimulation to improve heart function.

- **Tachycardia** possibly mediated by baroreceptor stimulation, helps to maintain cardiac output as stroke volume falls. Myocardial oxygen uptake is unfortunately increased by this.

All these mechanisms may become insufficient later and heart failure will ensue. The heart always strives to maintain myocardial wall tension within normal limits. The major determinants of myocardial oxygen consumption (MVO_2) are heart rate, contractility and ventricular wall tension. Wall tension may be expressed by the Laplace law:

$$\mathbf{T = (P \times R) / 2h}$$

T = tension of the heart
P = intraventricular pressure
r = radius of the heart
h = thickness of the muscle

Thus, MVO_2 increases with increase in heart size and intraventricular pressure, but hypertrophy will decrease wall stress. As soon as the increase in muscle thickness is negated by dilatation of the heart, wall tension will begin to rise and heart failure will set in. In patients with volume overload one finds that the ventricle starts to dilate at an early stage (i.e. increase in r) but there is also a concomittant increase in the muscle thickness (increase in h) i.e. hypertrophy takes place which will balance the increase in diameter. As soon as the dilatation exceeds hypertrophy, the heart will begin to fail.

A very simple, good correlate of MVO_2 is the product of heart rate (HR) and systolic blood pressure (SBP). This rate pressure product (RPP) is a measure of global MVO_2. It must be noted, however, that the HR and SBP have differential effects on overall myocardial oxygen supply/demand ratio. Increased HR will diminish oxygen supply to the heart because of relative decrease in diastolic time. Increased SBP, on the other hand, will, although it increases wall tension, also increase oxygen supply if the diastolic blood pressure increases with SBP.

It should be emphasized that the rate-pressure product appears to correlate more closely with oxygen demands in conscious patients subjected to exercise stress tests than it does in anaesthetized patients. Nevertheless, the rate-pressure product is a simple and useful clinical tool for the estimation of myocardial oxygen consumption. In normotensive or treated hypertensive patients, a general guideline would be to keep the rate-pressure product below a value ofr 12.000-14.000 in order to minimize increases in myocardial oxygen demand during anaesthesia.

The oxygen supply to the heart depends on two primary determinants:

- **Oxygen carrying capacity of blood.** Oxygen content of blood may be calculated by measuring haemoglobin content of blood and the PaO_2.

- **Coronary blood flow,** which is a function of coronary artery perfusion pressure and resistance. It is modulated by intravascular compression, HR, metabolic factors, atherosclerosis, certain drug effects, blood viscosity and neural and neurohumoral influences in the vascular tone of the coronary arteries.

By monitoring the ECG, myocardial ischaemia can be detected. The precardial lead V5 has been found the most helpful for detecting anterior and lateral ischaemia. Leads II, III and aVF are useful for inferior ischaemia. ST-segment changes may signify an imbalance in the oxygen supply/demand relationship. Significant (> 1 mm) elevation or depression in the ST segment is the best on-line measure, at present, of the presence of myocardial ischaemia.

Heart Pump Function

To understand the pump function of the heart one must briefly look at the phases of a cardiac ventricular cycle (figs. 3.3.2 and 3.3.3).

- The ventricle fills during diastole (phase I)

- after isovolumetric contraction (phase II)

- the ventricle ejects blood (phase III)

- and with isovolumetric relaxation (phase IV), the ventricle pressure rapidly decreases allowing the cycle to commence again.

Although 80% of left ventricular filling is passive, it is known that the other 20% is accounted for by the left atrial booster or "kick". This atrial contribution to ventricular filling

is important especially when a high cardiac output is needed during exercise, or when ventricular stiffness is increased. Loss of synchronized, powerful atrial contraction in such cases due to atrial fibrillation or atrioventricular dissociation, raises atrial pressure or lowers cardiac output or both. The best means of gauging cardiac function in disease is construction of pressure-volume loops to compute the end-systolic pressure-volume relationship. This relationship is linear and has been proved to be very sensitive to change in the contractile state while it is relatively insensitive to preload, afterload and heart rate. Unfortunately, it is still difficult to accomplish clinically since continuous measurement of pressures and volumes during sequential cycles are required.

At present, measurement of cardiac output is a more common method to monitor cardiac pump function. It should be realized that because many homeostatic reflexes influence cardiac output, it is a relatively insensitive measure of cardiac contractility, but cardiac output is the measure of cardiac pumping which is the ultimate function of the heart.

There are various invasive and non-invasive methods to determine cardiac output. Examples are:

- **Oxygen Fick technique:** this method is the calculation of pulmonary blood flow (cardiac output) calculated by the formula:

$$\mathbf{CO = (VO_2) / ((a\text{-}v)O_2)}$$

where:

CO - cardiac output L/min
VO_2 - total body oxygen consumption (inspired minus expired O_2 content)
$(a\text{-}v)O_2$ - arterial-mixed venous oxygen content difference

- **The indicator-dilution method:** this is the most versatile and most commonly used method of cardiac output determination. It involves injection of an indicator (dye or thermal) and measurement of the concentration time curve of the indicator. The formula used is:

$$\mathbf{CO = (I \times 60) / (Cm \times t)}$$

where:

CO -cardiac output in L/min
I - amount of indicator injected
Cm - mean indicator-dilution curve
t - total curve duration (sec)

The thermodilution method is easy to perform and several injections can be repeated within a short period. It is an invasive method which requires a thermistor-tippe pulmonary artery catheter. The measurement of cardiac output and determination of heart rate permits the stroke volume to be calculated:

$$\mathbf{SV = CO / HR}$$

The relationship CO = SV x HR is important to establish the relative contribution of HR and SV to cardiac output, which is important in assessing the pump function of the heart. Myocardial function can be impaired if CO has to be maintained by high HR and low SV.

Heart work can be calculated by computing the stroke volume times the pressure at which the blood is ejected. If stroke work is indexed for body size, the following formula is used to determine stroke work index:

LVSWI = (MAP - PCWP) x SVI x 0.0136 gm/M^2/beat

where:

SVI = SV/BSA in mL/M^2 = Stroke volume index
BSA = body surface area (M^2)
MAP = mean systemic pressure (mm Hg)
PCWP = pulmonary capillary wedge pressure (mm Hg)
0.0136 = conversion factor (mm Hg x cm^3 to g x m)

The calculation of LVSWI is useful when estimating external left ventricular work and when plotted against the PCWP it describes left ventricular performance.

An indirect measure of adequate pump function is systemic pH and tissue oxygen extraction. Properly oxygenated tissues will not cause acidosis, nor will venous blood saturation fall profoundly. Although there are many causes of arterial acidosis, certainly low cardiac output is one. Because tissue perfusion and oxygenation are the ultimate measures of the adequacy of cardiovascular function, evaluation of organ function will give an indication of cardiovascular performance.

CNS = mentation, consciousness, pupils, reflexes, EEG

Heart = ECG: ischaemia, dysrhythmias; CO: pumping function

Kidney = urine volume, concentration, composition

Skin = colour, temperature, capillary refill

Lung = shunt, $AaDO_2$, dead space

Of course, tissue oxygenation and function also depend on factors other than perfusion, i.e. blood oxygen content, ventilation, nutrition, temperature, etc.

Haemodynamics of Heart Failure

The right heart circulation, responsible for pulmonary perfusion, is a low pressure system and therefore thinner walled than the left heart circulation which is a high pressure system. Despite the differences in pressures, work load, wall tension and oxygen consumption between the right and left ventricles they both pump the same volume of blood per minute. Also, the coronary flow to the right heart peaks during systole, whereas the peak bloodflow

to the left ventricle occurs in diastole.

Underlying all concepts of muscle mechanics is the Frank Starling mechanism which relates the degree of muscle stretch to the intensity of muscle contraction. Within limits, the more initial stretch there is, the greater the contraction will be. Clinically one can correlate this with higher filling volumes or pressures, enhancing myocardial ejection. The filling volume is often termed preload, which in the normal ventricle may be considered the end-diastolic pressure (fig. 3.3.4).

The next factor which influences the force of contraction is the inotropic state of the ventricular muscle expressed as contractility. Contractility of myocardial fibres is the ability of the ventricular muscle to generate pressure at a constant preload. This property of the muscle can be increased by positive inotropic drugs and decreased by disease and negative inotropic drugs.

The ventricles contract against forces which oppose shortening. These forces which will also increase the systolic wall tension are mainly the systolic pressure in the vascular tree, high systemic resistance and aortic stenosis.

Optimal ventricular performance thus depends on a proper balance between the primary determinants of muscle mechanics namely preload, afterload, contractility, heart rate and heart rhythm. In clinical practice measurement of cardiovascular variables are therefore necessary:

- **Heart rate**

Since CO = SV x HR, a low CO can result from a low HR, especially in certain conditions such as aortic stenosis, end-stage LV failure, etc. A very fast HR can reduce ventricular preload by limiting diastolic filling time. This is especially important in conditions such as mitral or tricuspid stenosis. A high HR may adversely distort myocardial oxygen balance (elevated demand, lowered supply) and ischaemia impairs ventricular function (lowered compliance, lowered contractility).

- **Heart rhythm**

Lack of a co-ordinated cardiac cycle reduces CO and SV, lowers BP, and can start a progressive myocardial oxygen imbalance as well as decreasing ventricular function.

- **Preload**

This is equated with left ventricular end-diastolic pressure or pulmonary capillary wedge pressure.

- **PCWP**

This is the most accurate, commonly used clinical tool for estimating left ventricular preload. The PCWP is a reflection of the left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP) under certain conditions. In the presence of mitral stenosis, severe

left ventricular hypertrophy and postmyocardial infarction it is difficult to estimate LVEDP from LAP. Pulmonary hypertension makes PCWP a spurious measure of LAP.

- **CVP**

Just as the LAP is an estimate of left ventricular preload, the central venous pressure is an estimate of right ventricular (RV) preload and important to monitor during RV dysfunction or pulmonary hypertension.

- **Afterload**

This is equated with systolic arterial pressure or systemic vascular resistance.

- **SVR**

Systemic vascular resistance = ((MAP - CVP)/CO) x 80 dynes·sec·cm^{-5}

- **PVR**

Pulmonary vascular resistance = ((MPAP - PCWP)/CO) x 80 dynes·sec·cm^{-5}

where MPAP = mean pulmonary artery pressure. Knowledge of these respective resistances is useful in making decisions regarding use of vasoactive drugs to improve the patients haemodynamic function.

- **Contractility**

This is much more difficult to assess. Several means have been employed for this purpose, i.e. maximal velocity of ventricular shortening (Vmax), ventricular dP/dt and ventricular ejection fraction (EF). The main limitation of all these is their sensitivity to load and heart rate. Clinically, ejection fraction is considered a reliable and relatively easily derived measure of global ventricular function. Ejection fraction is computed by the formula:

$$\mathbf{EF = (EDV - ESV) / EDV}$$

where: EDV - end-diastolic volume
ESV - end-systolic volume

These volumes can be determined by use of echocardiography, isotope imaging and a specially adapted thermodilution pulmonary artery catheter. The EF is expressed as a percentage, with a normal value of ± 60%. It is important to consider preload, afterload and HR when interpreting EF.

For any given preload and inotropic state the degree of fibre shortening will be indirectly related to afterload, i.e. with increasing afterload a larger proportion of the muscle's contractile activity will be spent on building tension and a lesser portion on muscle shortening, resulting in a decrease in stroke volume. The normal heart is more dependent on preload than afterload to maintain cardiac output. In the failing heart the afterload is critical

to such an extent that a small increase in afterload can decrease the cardiac output.

There is also a relationship between preload and afterload. Because afterload is a function of intraventricular pressure as well as volume, any venodilator that decreases the preload will also decrease intraventricular volume and therefore also the afterload, without any deleterious effect on peripheral resistance. An arterial dilator decreasing arterial pressure will decrease afterload and therefore facilitate ventricular emptying resulting in an increased stroke volume. The decrease in end-diastolic volume will decrease end-diastolic pressure and thus the preload.

In heart failure the decreased cardiac output results in an increased afterload due to neural, humoral and structural changes in the arterial bed. Dilatation of the heart contributes to the increased afterload while it increases the oxygen requirements and lowers cardiac ouput. Afterload is therefore an important determinant of cardiac output in patients with cardiac failure.

In patients with mitral incompetence the regurgitation fraction will vary directly and the anterograde stroke volume indirectly with the afterload. The response of the ventricle to an increase in afterload is directly dependent on myocardial contractility. If this is normal, stroke work will increase while there is little change in end-diastolic pressure. When contractility is lowered, stroke volume will decrease markedly while end-diastolic pressure will rise. Measures to lower preload will be most useful in patients with pulmonary oedema due to for instance mitral stenosis where the venous feedback from the lungs should be decreased.

The terms decreased myocardial contractility or contractile failure must be used with some precision to enable one to develop adequate therapeutic approaches. It is clear that a reduced stroke output is good clinical evidence for ventricular failure. But we need to distinguish contractile failre from hypovolaemic or mechanical causes, and we need to separate right ventricular from left ventricular failure. On the other hand, a normal stroke output may reflect inadequate ventricular reserve in certain circumstances, for example in cases with sepsis.

Similarly, an elevated pulmonary capillary wedge pressure may suggest ventricular failure or fluid overload, or mechanical obstruction or increased ventricular stiffness. In contrast, a normal pulmonary capillary wedge pressure may be found in a failing, dilated ventricle with increased compliance. In order then to diagnose depressed cardiac contractility, ventricular end-diastolic volume must clearly be elevated, and total stroke volume and/or cardiac index and work should be reduced or normal while heart rate and afterload are normal.

The Sympathetic Nervous System and Heart Failure

It is a well-known fact that release of norepinephrine in the myocardium strengthens the inotropic state of the myocardium, especially the contribution of heart function during exercise or episodes of acute stress. During the early stages of heart failure urinary catecholamine excretion increases. With time the myocardial catecholamine stores are depleted, not only because of loss into the circulation but also because there is decreased

synthesis and uptake in the terminal neurons. It has also been shown that the beta-receptor population is decreased in advanced congestive heart failure. This may be due to down-grading of the receptors in response to pronged stimulation. Therefore, although cardiac stores of norepinephrine are not fundamental to maintenance of the intrinsic contractile state of the myocardium, diminished release of the neurotransmitter and of beta-receptor density in heart failure may be responsible for loss of the much-needed adrenergic support of the failing heart and in this manner could intensify the severity of the congestive heart failure state. As a result of this the myocardium does not respond to the increased levels of circulating norepinephrine and it explains why beta-agonists may have little effect in progressive heart failure. Stimulation of the adrenergic system also leads to tachycardia and this is often the first sign of heart failure.

Neurohumoral Changes During Heart Failure

Cardiac output is lowered due to severe cardiac failure. Arterial blood pressure is maintained by an increase in systemic vascular resistance which is initially achieved by alpha-adrenergic stimulation and later by increased angiotensin levels in the circulation. Recently it has also been shown that there is a twofold increase in arginine-vasopressin in most patients with CHF. It is presumed that sympathetic activity, plasma renin-angiotensin activity and arginine-vasopressin evolved as separate but interrelated functional units designed in part to maintain perfusion pressure and retain circulating volume in the face of inadequate blood flow. Although these systems are probably under different control mechanisms, they facilitate each other's biological activities and share the common properties of vasoconstriction and antidiuresis. Increased SVR increases the afterload and thus the heart's workload and ultimately MVO_2. The unanswered question is whether these systems overcompensate in CHF, resulting in circulatory congestion and increased vascular impedance on a myocardium that is already operating under stress.

Initially cardiac output is curtailed only during exercise but later also during rest. At that stage the angiotensin mechanism is employed to help to redistribute the diminished cardiac output. Due to redistribution of blood flow, renal perfusion decreases and this leads to retention of sodium and water, which is followed by the edematous phase of heart failure. The drop in renal blood flow causes secretion of renin and then angiotensin II which is a potent vasoconstrictor and also stimulates secretion of aldosterone with further retention of salt and water. This is the reason why the total blood volume, the interstitial volume and total body sodium are usually increased in patients suffering from heart failure (fig. 3.3.5).

Although many of the clinical signs and symptoms of congestive heart failure are secondary to excessive fluid retention, the expansion of blood volume remains one of the important compensatory mechanisms that helps to maintain cardiac output by elevating ventricular preload, according to the Frank Starling mechanism, except in the terminal stages of heart failure.

Due to the increased sodium and water retention, vascular sodium content is increased and interstitial pressure is raised. This leads to increased vascular stiffness which impairs the normal metabolically induced vasodilatory mechanisms. Muscle ischaemia due to poor perfusion during exercise leads to anaerobic metabolism, lactic acidaemia, excessive oxygen debt, weakness and fatigue. Patients with heart failure usually also have constricted veins in

their extremities, resulting from increased interstitial and tissue pressure which compress the veins, the high levels of circulating catecholamines and angiotensin II, as well as the activity of the sympathetic nervous system.

Vasoconstriction and fluid retention are appropriate homeostatic responses in cases with circulatory failure due to hypovolaemia, but in congestive heart failure that are inappropriate, since preload and afterload are further increased and this may lead to further deterioration of cardiac function. The neurohumoral response may trigger a vicious circle in which cardiac function is adversely affected, tissue perfusion is impaired further and this stimulates the neurohumoral mechanisms even more. In this regard it is interesting to note that recentrly increased levels of atrial natriuretic peptide (ANP), a hormone secreted by the heart causing natriuresis, diuresis and vasodilation, has been documented in heart failure. ANP is secreted in response to increased atrial volume and tachycardia and may provide a counterbalance to the increased salt and water retention seen in heart failure.

Mechanism of Depressed Myocardial Contractility

It is clear that congestive heart failure is the end result of a large number of different chronic processes such as ischaemic heart disease, valvular heart disease, hypertension, cardiomyopathy, and high-output states such as thyrotoxicosis. Nevertheless, it is still not clear how the inotropic state of the myocardium becomes impaired in the first instance. Despite considerable effort and innumerable studies, the fundamental mechanism causing the decrease in useful external work of the myocardium in low-output heart failure is still not clear. Confusing and conflicting evidence for the mechanism of failure has been found in studies analysing energy supply, production, storage and utilization, as well as the function of the contractile proteins and ultrastructural changes. Although a number of defects in these have been delineated, it is not clear which is the primary defect responsible for heart failure and which are secondary compensatory mechanisms. Thus, no unifying biochemical defect responsible for heart failure has been identified as yet, but there is evidence for several possible defects. The reasons why the myocardium is defective are probably multiple and may include:

1. Distortion and destruction of sarcomere structure by undue stretching in congestive failure. This could fit in with the concept of long-continued overwork.

2. Decrease in myosin ATP-ase activity.

3. Changes in Ca++ metabolism with regard to the delivery of Ca++ for initiation of contraction, or in determining the contractile state.

4. Available evidence suggests that it is unlikely that changes in mitochondrial function are casually related to the development of heart failure. They may well play an important role in perpetuating chronic heart failure. The major clinical problem relates to the increased oxygen uptake required by the large dilated heart.

Functional Classification of Congestive Heart Failure

The Goldman Risk Index

In a retrospective study of 1001 patients, Goldman identified nine independent significant correlates of serious cardiac complications. From these he developed a scoring system for cardiac risk factors (tables 3.3.3 and 3.3.4). This scoring system provides a valuable reference to assess risk pre-operatively in view of the patient's medical status. It also identifies factors which may be altered by treatment and thereby reduce risk.

Table 3.3.3. Goldman index risk factors

Factor	Score
Signs of congestive heart failure	11
Myocardial infarction in the past 6 months	10
Premature ventricular beats (> 5/min)	7
Other than sinus rhythm	7
70 or more years old	5
Emergency surgery	4
Vascular, intrathoracic or upper abdominal surgery	3
Aortic stenosis	3
Poor general condition	3
Total	53

Table 3.3.4 Goldman cardiac risk index

Class	Point total	No or minor compl	Life threat compl	Cardiac deaths
I	0-5	99%	0.7%	0.2%
II	6-12	93%	5%	2%
III	13-25	86%	11%	2%
IV	26	22%	22%	56%

New York Heart Association Classification

Early in the course of congestive heart failure, intrinsic myocardial contractility is sufficient to generate normal and moderately increased levels of cardiac output. Asymptomatic patients are New York Heart Association (NYHA) functional class 1. The heart's capacity to increase its contractile performance (inotropic reserve) in respone to increasing demands for O_2 delivery becomes progressively limited. During periods of increased metabolic need, the compensatory mechanisms are invoked to increase cardiac output. Thus, patients in early stages of heart failure will be symptomatic only during and immediately after moderate exercise (NYHA class 2). With moderate disease, cardiac output is normal at rest only as a result of an elevated end-diastolic volume and sympathetic activity. Less reserve remains in these compensatory mechanisms, and therefore, little inotropic reserve. This patient becomes symptomatic when metabolic demands exceed resting levels during ordinary physical activity

(NYHA class 3). In patients with severe congestive heart failure, cardiac output is insufficient to meet normal resting metabolic demands despite compensatory mechanisms utilized to their full potential. There is no remaining inotropic reserve. These patients are symptomatic at rest and any physical exertion increases their symptoms (NYHA class 4).

Invasive Monitoring

Many patients older than 65 have unrecognized, severely compromised cardiac function and impaired oxygen delivery which can be identified only by aggressive invasive monitoring. This approach makes it possible to estimate myopcardiacl efficiency by measuring cardiac output, as well as left and right-sided filling pressures and then constructing Starling curves. The total efficiency of the cardiovascular system can be estimated by calculating haemodynamic and oxygen transport variables.

The Forrester Diagram

Based on their pulmonary capillary wedge pressure and cardiac index, patients with cardiac dysfunction can be arranged into several groups (fig. 3.3.6). These four groups or quadrants provide a simple method of categorization and a basis for subsequent therapy.

The cut-off points are chosen because:

- **PCWP**

Beyond 20 mm Hg pulmonary hydrostatic pressure will cause pulmonary congestion. A wedge pressure of 18 mm Hg is still "safe" and should not cause congestion yet allow utilization of the Starling mechanism to enhance cardiac output.

- **CI**

In the awake patient a CI below 2.2 L/min/M^2 is usually associated with clinical signs of hypoperfusion. During anaesthesia metabolism is slower and cooling is present. An even lower CI might be adequate in this setting.

The goals of preoperative evaluation are to:

- recognize clinical signs of congestive heart failure in order to identify patients with myocardial dysfunction

- define the underlying cause of myocardial failure

- determine whether the patient's cardiovascular function and therapy reach their achievable potential

Symptoms and Signs

Symptoms

Due to Pulmonary Congestion

- **Dyspnoea,** especially with exercise, is classified as:

- Grade I: a patient with cardiac disease and dyspnoea during moderate exercise but no previous history of complaints

- Grade II: short of breath during normal everyday exercise, i.e. walking on level surfaces, climbing stairs, making beds

- Grade III: short of breath after slight exertion, i.e. undressing, climbing in or out of bath

- Grade IV: short of breath during rest

- **Orthopnoea:** the patient feels better when sitting up or lying in Fowler's position

- **Paroxysmal nocturnal dysnpoea (PND):** an intense dyspnoea occurring at night due to attacks of pulmonary oedema. The patient wakes up with a slight cough and may even produce red, bloody sputum at a later stage. It occurs usually more or less two hours after retiring and continues for about 20 minutes.

Symptoms due to Systemic Congestion

- Oedema of the legs and later the lower half of the body with anasarka

- Tenderness in the right hypochondrium due to congestion of the liver with stretching of the liver capsule

- Anorexia, vomiting and loss of appetite due to congestion of the mucosa of the gastrointestinal tract

Lowered Cardiac Output With

- Cerebral symptoms such as depression, irritability, forgetfulness, loss of concentration and intellectual deterioration

- General tiredness and apathy due to poor tissue oxygenation

- Peripheral cyanosis due to delayed circulation via the capillaries with increased O_2 extraction, seen especially in the fingers, nose, lips and toes

- Oliguria secondary to lowered renal blood flow

These symptoms cannot simply be accounted for in terms of the compensatory neuroendocrine response to congestive heart failure. It is partly due to changes within the microvasculature of the endothelial cells or smooth muscle. This poorly understood phenomenon is critical in chronic congestive heart failure because it almost certainly accounts for the reduced blood flow to skeletal muscle during exercise thus giving rise to the symptoms described above that limit the performance of the patient with congestive heart failure.

Respiratory Complaints Including

- Coughing due to congestion of the bronchial mucosa

- Haemoptysis because of pulmonary oedema with expectoration of light red discoloured frothy sputum. Pussy and blood-stained sputum occur due to recurrent pulmoary infections. Mucoid sputum with blood-staining may occur after a pulmonary embolus. Bright red blood may occur after rupture of a congested pulmonary submucosal vein.

Left or right heart failure can usually be determined from the history. Patients with left heart failure will have more complaints of pulmonary congestion, lowered cardiac output as well as many respiratory complaints. On the other hand, patients with right heart failure will mainly have complaints of oedema and congestion of the gut (tender liver, nausea, and loss of appetitite).

Physical Signs

Left Heart Failure

Signs of the aetiological factor in the form of hypertension on heart murmurs are often present. If no clear cause can be found on clinical examination, special investigations may assist in the diagnosis.

The following changes may be found on examination:

Pulse

- Tachycardia of unknown origin

- Pulsus alternans

- Small pulse volume

- Dysrhythmias

The Skin

- Peripheral cyanosis

- Cold, clammy skin

- Atrophic skin

Cardiac Examination

- *Size:* the heart may be enlarged depending on the duration of onset of heart failure.

- *Hypertrophy:* left ventricular hypertrophy is usually present in cases where volume or pressure overload plays a role.

- *Heart murmurs:* the presence of a murmur does not necessarily indicate its aetiologic importance. In patients with severe cardiomegaly, mitral or tricuspid incompetence may develop due to dilatation of the valve ring, and need not be the cause of heart failure *per se.* Aortic incompetence never develops secondary to cardiac dilatation, and is usually pathological in nature.

- *Heart sounds:* a third heart sound in conjunction with a gallop rhythm is always abnormal and may precede other signs of impending heart failure. In persons younger than 30 a third heart sound is not necessarily abnormal. The importance of a K3 must be evaluated against the background in which it occurs. A K4 is not a sign of heart failure, but a sign of lowered myocardial compliance.

- *Pulmonary signs:* Cheyne-Stokes breathing is a sign of advanced heart failure. It is not pathognomonic, however, and may occur with most types of heart failure.

Early inspiratory crepitations occur especially over the basal areas of the lungs. Initially, it is only basal but as heart failure progresses, it can be heard progressively higher in the lungs. It must be distinguished from normal crepitations which often occur in bedridden patients. If these patients breathe in deeply or cough, their crepitations disappears, while the pathological crepitations present in heart failure do not disappear. They may become more coarse as heart failure progresses. In patients with pulmonary oedema bubbling sounds are clearly audible.

Ronchi may be present and the picture may mimic bronchial asthma. This usually occurs in patients who are developing pulmonary oedema. These signs are usually found in left ventricular failure. However, it is rare to find left ventricular failure in isolation - usually there are concomittant signs of right heart failure as well. In certain patients, especially those with an acute onset, the signs of left ventricular failure are more prominent and the signs of righ heart failure usually appear only at a later stage.

Right Heart Failure

The commonest cause of right heart failure is left heart failure. The next most common cause is probably pulmonary pathology, i.e. emphysema. When right heart failure develops secondary to lung pathology, the condition is called *Cor pulmonale.*

The following signs may be found:

- The pulse may be normal or dysrhythmias may occur.

- Neck veins are usually clearly congested in patients with right heart failure. Normally, the a-c-v waves can be distinguished with ease and there may even be aberrations in these waves due to the underlying pathology. With tricuspid incompetence there will be prominent c-v waves and with pulmonary hypertension the a wave will be clearly visible. In normal patients pulsations in the neck veins are visible for 3-4 cm above the sternal angle if the patient is in a 45 degree sitting position. Jugular venous pulsation visible more than 4.5 cm above the sternal angle is always abnormal. It is sometimes profitable to study the neck veins in relation to breathing. In patients with lung disease the neck veins may be congested but will collapse almost completely with inspiration, only to reappear with expiration. In the patients with heart failure as well, the neck veins will diminish slightly but they do not disappear completely during inspiration. In patients with constrictive pericarditis or cardiac tamponade the veins are usually tremendously congested and during inspiration the congestion will increase even more instead of decreasing (Kussmaul's sign). It is important to remember that neck vein congestion is a sign of right heart failure and not of left ventricular failure.

Cardiac Examination

- Right ventricular hypertrophy may be present, but may not be detectable because of underlying pulmonary disease.

- A right ventricular gallop is sometimes present and can be distinguished from a left ventricular gallop because of accentuation during inspiration.

- Heart murmurs may indicate primary valvular disease as the cause of cardiac failure. Murmurs of mitral or tricuspid regurgitance may also be seondary to dilatation of the respective ventricles.

Pulmonary Signs

- The signs of the underlying lung disease are usually more prominent when cor pulmonale is present.

- Inspiratory crepitations are not a sign of right heart failure.

- A pleural effusion, usually right-sided, and sometimes bilateral, may occur with right or left sided failure.

Ankle Oedema

Oedema usually starts in the legs as the disease progresses, generalized oedema (anasarka) may develop. Ascites usually indicates a severe degree of right heart failure.

Hepatic Congestion

The liver is usually enlarged with a smooth surface and a tender edge. If tricuspid incompetence is present, the liver will pulsate on palpation. A slight degree of jaundice may also be present due to liver dysfunction. In cases with chronic hepatic congestion, a form of liver cirrhosis may develop.

Diagnosis of Heart Failure

In most cases the diagnosis of heart failure is made clinically. Special investigations are used to confirm the clinical diagnosis or to try and determine the cause of heart failure.

Chest X-Rays

In cases with chronic left heart failure enlargement is diagnosed radiologically when the diameter of the heart on the postero-anterior exposure exceeds 50% of the chest diameter. The earliest changes are seen in the lungs when redistribution of blood flow to the upper lobes begins to develop. As the pulmonary veins become congested, fluid begins to exude into the alveoli and also begins to accumulate in the walls of the bronchial vessels as well as in the inter lobular septae with the appearance of Kerley B lines. As the condition progresses, the intra alveolar fluid increases until pulmonary oedema develops with the typical "angel wing" appearance.

In right heart failure hypertrophy and dilatation of the right ventricle can be detected on the lateral chest film. A prominent retrosternal fullness can be seen due to right ventricular hypertrophy and sometimes distension of the pulmonary outflow tract as well. The underlying lung disease which caused the right heart failure can usually be detected as well.

Electrocardiography

This makes no direct contribution towards the diagnosis of heart failure. In some cases an aetiological factor such as acute or chronic ischaemic heart disease, left ventricular hypertrophy or dysrhythmias may be identified.

Echocardiography

This is especially useful to diagnose rheumatic valvular lesions. Most of the valvular lesions have typical patterns. A myopathic ventricle can also be detected with ease although the precise cause of the myopathy cannot always be shown.

Radionuclide Studies

The most common radionuclide examination used in heart failure is the determination of left ventricular ejection fraction. It is also possible to determine right ventricular ejection fraction but it is more difficult technically. The normal LVEF is 55% or more. In cases with borderline values an exercise test can be done to examine the ventricle's response to exercise. Normally an increase of 5% can be found. If this increase is not found, left ventricular dysfunction can be diagnosed.

Invasive Monitoring

In selected cases it may be necessary to use heart catheterization or selective right heart catheterization, with the aid of a percutaneous transvenous flow-directed pulmonary artery catheter. Although this does not contribute to diagnose the aetiology of heart failure, it can determine the degree of failure with reasonable accuracy.

Management of Cardiac Failure

Patients requiring surgery may present with varying degrees of cardiac or cardiovascular compromise due to any of the many different mechanisms or causes discussed in this chapter. Most often it is an elderly patient with chronic congestive heart failure who may be mildly, moderately or severely compromised according to the NYHA functional classification, who needs elective or emergency surgery. On the other hand it is not uncommon to diagnose acute ventricular failure in the perioperative period and patients may even present with cardiogenic shock. It is a basic principle that therapy should be based on a thorough understanding of the pathophysiology of the underlying cardiac or cardiovascular disease. The many aetiologies and degrees of severity of the heart failure syndrome would then demand an individualized approach to each patient. Fortunately certain general principles apply to the management of various subsets of patients (fig. 3.3.7) because although cardiac failure has multiple aetiologies, a common pathophysiologic pathway depending on the compensatory mechanisms can usually be recognized.

As a general rule the first priority in treatment is to eliminate or remove underlying cause, if possible. This includes measures such as surgical repair of valvular lesions or medical treatment of hypertension or infective endocarditis.

In the second instance, precipitating factors which can tip the balance of the compromised heart towards decompensation should be removed (table 3.3.5).

Table 3.3.5. Precipitating Factors in Congestive Heart Failure

1. Increased demand

- Anaemia

- Infective endocarditis

- Bacterial infections

- Fluid overload

- Thyrotoxicosis

- Arteriovenous shunt

- Renal failure

- Hepatic failure

- Respiratory insufficiency

- Obesity

- Pregnancy

2. Dysrhythmias

3. Pulmonary embolism

4. Ethanol ingestion

5. Vitamin deficiency (thiamin)

6. Uncontrolled hypertension

7. Drugs

- Beta-adrenergic blockers

- Anti-arrhythmic drugs

- Salt-retaining drugs

Thirdly, treat the clinical manifestations of heart failure of patients in NYHA functional class II to IV (table 3.3.6).

Table 3.3.6. Strategy for Management of Congestive Heart Failure

1. Remove specific underlying cause

2. Remove or treat precipitating cause

3. Treat clinical manifestations

3.1 Measures to improve contractile performance

- Inotropic drugs

- Sympathomimetic drugs

- Pacemaker

3.2 Measures to reduce cardiac work

- Rest

- Correct obesity

- Vasodilator drugs

- Assisted circulation

3.3 Measures to control salt and water retention

- Limit dietary sodium intake

- Diuretics

- Mechanical removal of fluid

Usually the first recommendation will be judicious limitation of activity, tailored to the severity of the heart failure. Increased restriction of activity is usually necessary as heart failure progresses. Bed rest is of importance for patients with severe heart failure (class III) as it decreases the body's oxygen consumption and therefore the workload of the heart as well. It is impractical to restrict the patient to bed for prolonged periods. Deep venous thrombosis with pulmonary embolism is an ever present threat. Patients should be mobilized as soon as possible but advised to avoid physical exertion.

Table 3.3.7. Drug Treatment of Heart Failure

A. Mild heart failure

- Diuretics alone

a. Hydrochlorotiazide 25-100 mg/day. May require potassium supplementation.

b. Potassium sparing combinations: Amiloride 5 mg + hydrochlorothiazide 25 mg 1-2 tabs/day.

B. Moderate heart failure

- Furosemide 20-600 mg/day. Needs potassium supplementation.

- Furosemide + spironolactone 25-200 mg/day, if more than 80 mg of furosemide is required daily.

- Angiotensin converting enzyme inhibitor (ACE)

- Captopril 50-100 mg/day

- Digoxin < 70 years : 0.25 mg/day

> 70 years : 0.125 mg/day

- Add nitrates if congestive symptoms are marked, but stop spironolactone first.

- Isosorbide dinitrate 10-60 mg PO every four hours.

- Anti-arrhythmics if indicated.

C. Severe heart failure

- Furosemide

- Digoxin 0.75-1.00 mg IV, in divided doses to digitalize patients.

- ACE inhibitors or a combination of

- Hydralazine 10-75 mg every 6 hours and

- Isosorbine dinitrate

- Anti-arrhythmics if indicated.

D. Acute left ventricular failure

- Circulatory volume: Until one is certain of the fluid status only low doses of diuretics should be given. Adequate circulating volume is important to maintain cardiac output (preload reserve).

- Inotropic therapy:

Digoxin: Rarely indicated except for atrial fibrillation.

Dobutamine: Infusion 5-15 microg/kg/min. Drug of choice.

- Vasodilators:

Isosorbide dinitrate

Nitroglycerine infusion: 10-100 microg/min

- Nitroprusside infusion: 5-150 microg/kg/min. Furosemide intravenous.

E. Refractory heart failure

- Exclude possible aggravating factors.

- Invasive haemodynamic monitoring.

- Dobutamine infusion (titrated to the desired haemodynamic effect).

- Dopamine infusion (titrated to the desired haemodynamic effect).

- Furosemide

- Potassium and Magnesium supplementation.

- Mechanical assist devices.

- Cardiac transplantation.

Patients with class II failure may require a diuretic or cardiac glycosides. In many cases modest doses of digoxin and a mild diuretic such as dyazide will restore the patient to an essentially asymptomatic state. Digoxin remains the prototype of inotropic agent. It causes a mild positive inotropic action and has a negative chronotropic effect. It improves myocardial contraction especially in cases where the left ventricle is dilated. In patients with cardiomyopathy or disease of the myocardium, it seems to be less effective than in cases with heart failure due to valvular lesions. It is also very useful in patients with supraventricular tachydysrhythmia. In these cases it will delay the ventricular response with improvement of the cardiac output. The mean dose for adults younger than 70 with normal renal function is 0.25 mg/day. In older patients with impaired renal function the dose has to be adjusted accoring to renal function and blood levels of digoxin.

Patients who are susceptible to the toxic effects of digoxin are:

- Elderly patients with less muscle mass

- Patients with impaired renal function

- Hypoxaemic patients

- Patients with hypothyroidism

- Patients with hypokalaemia and hypercalcaemia

The general consensus today is that digoxin is probably not of major importance for patients with heart failure who are in sinus rhythm. This group of patients can usually be managed satisfactorily with other drugs, such as vasodilators or newer and more potent inotrope-vasodilators. In patients with severe heart failure, where inotrope support is indicated, intravenous inotropes such as dobutamine or dopamine are effective. Dobutamine is usually the drug of choice at a dose of 5-10 microg/kg/min. Dopamine may be added in low doses

(2-5 microg/kg/min) to increase renal perfusion in hypotensive patients.

As far as diuretics are concerned, the first line drug is usually thiazide diuretic, which causes loss of salt and therefore also water. Unfortunately it can also cause hypokalaemia and hypomagnesaemia. The excessive fluid retention of heart failure can therefore be managed successfully with these drugs. However, the diuretic used most often in heart failure is furosemide, at a dose of 40-120 mg/day. If used over a long period, potassium supplementation will be necessary - especially if digoxin is administered simultaneously. Although furosemide is primarily a diuretic, it also has a direct venodilatory effect which starts to act much earlier than the diuretic effect. After oral intake diuresis will start after three to four hours.

Another useful diuretic is the aldosterone antagonist, spironolactone. At 100-200 mg/day this drug promotes sodium excretion, but retains potassium. Renal function and serum potassium have to be monitored when patients are given this drug. The diuretic effect starts only after 48-72 hours, and the dose should therefore not be adjusted too soon.

Most diuretics tend to cause loss of electrolytes. Salt retention should therefore not be a major problem and rigid dietary salt restriction can usually be avoided until diuretics can no longer control the accumulation of salt and water.

As the severity of heart failure increases, the diuretic regimen can be intensified or vasodilators may be added. Vasodilators have introduced a new era in the treatment of acute as well as chronic heart failure. Drugs may be divided into:

- arterial vasodilators, such as nifedipine, huydralazine and alpha-blockers

- venodilators, such as nitrates, diuretics and morphine

- drugs with a combined effect such as nitroprusside, prazosine and captopril

Arterial vasodilators are used especially to decrease the high peripheral resistance of heart failure. Decreasing resistance or afterload increases cardiac output and stroke volume. Most of these drugs can be given orally and will take effect within hours. Although these drugs are used primarily for hypertension, they do not seem to have a hypotensive effect unless prescribed in very large doses. The most important effect of arterial vasodilators are the improvement in the heart's ejection fraction.

Venodilators cause pooling of blood especially in the venous capacitance vessels. Fluid shifts from the lungs to the periphery to improve pulmonary congestion. If used in patients without pulmonary congestion, the ventricular preload will be suboptimal and cardiac output will decrease. These patients tend to develop tachycardia and hypotension. Venodilators are very useful in patients with pulmonary congestion and pulmonary oedema.

Vasodilators which act on veins and arteries will have a combined effect. Prazosine can generally be seen as the oral form of nitroprusside. The disadvantage of nitroprusside is that it can be administered only intravenously, while the advantage is that it acts immediately and has a very short half-life. Doses can therefore be adjusted with precision. A pulmonary

artery catheter is usually necessary for haemodynamic monitoring when using nitroprusside.

The angiotensin converting enzyme inhibitors (ACE-I) are competitive antagonists of angiotensin-converting enzyme. The role of angiotensin and aldosterone has been discussed already. The ACE-I most extensively studied in cardiac failure is captopril. Although this drug has originally been promoted as an antihypertensive drug, its vasodilatory properties are becoming more important for management of congestive heart failure. It is very effective, even in patients with refractory heart failure. The starting dose is usually 6.25 mg/day which can then be increased gradually to a dose of 100 mg/day. Hypotension can develop in patients using large doses of diuretics. A low-dose diuretic is usually effective to control oedema when using captopril. The newer ACE-Is are also effective in the treatment of congestive cardiac failure.

Refractory and Intractable Heart Failure

Refractory heart failure is present when it persists or worsens despite intensive therapy, whereas intractable heart failure is defined as failure resistant to all known therapeutic measures.

The first step in patients with refractory heart failure is to exclude any treatable underlying cardiac or non-cardiac condition carefully. Potentially correctable cardiac causes include rhythm disturbances, ventricular aneurism, valvular disease, coronary artery disease, infective endocarditis, constrictive pericarditis and cardiac tumours.

There are many non-cardiac conditions as well which may render heart failure resistant to therapy unless corrected, i.e. anaemia, electrolyte disturbances, pulmonary or systemic infections, pulmonary embolism, hyper- or hypothyroidism and over- or undertreatment with drugs such as digitalis, diuretics or vasodilators.

Only after excluding every possible aggravating factor carefully and after therapy has been considered and optimized meticulously can heart failure be considered intractable.

In these patients other forms of therapy should be considered. These include the use of mechanical circulatory support such as intra-aortic balloon counterpulsation or cardiac transplantation. Intra-aortic balloon counterpulsation is a temporary measure and is therefore only indicated to support cardiac function while a potentially reversible condition is being treated. The main indications are to stabilize patients with:

- acute valvular lesions

- ventricular septal defects before surgical repair

- preinfarction angina which does not respond to medical therapy while the patient is awaiting surgery

- cardiogenic shock that is potentially reversible

- unstable postcardiac-surgery patients.

Arrhythmias

Arrhythmias are common in all forms of heart failure especially in those patients with dilated cardiomyopathy and ischaemic cardiomyopathy. Arrhythmias such as atrial fibrillation, junctional rhythm or AV dissociation where atrial contraction does not precede ventricular contraction may be associated with heart failure in these patients with marginal cardiac reserve. They cannot tolerate the 20-25% reduction in cardiac output resulting from loss of the atrial "kick". Arrhythmias may be responsible for sudden death in these patients.

Control of heart rate and rhythm is therefore an important step tgo enhance cardiac function and efforts to restore sinus rhythm should precede other therapeutic maneuvres.

Extremes of rate or any rhythm that do not result in normal sequential atrioventricular contraction should be treated. This will be discussed in section II of this chapter.

Acute Pulmonary Oedema

Acute pulmonary oedema due to increased left ventricular preload is a medical emergency which must be differentiated from the adult respiratory distress syndrome (ARDS). It would be totally inappropriate to reduce preload and thus cardiac output in the latter condition, while it is a therapeutic priority during the management of acute pulmonary oedema. For this reason arterial and pulmonary artery catheterization should be performed in all cases of severe left ventricle failure. While invasive monitoring of bloodgases, PCWP and MAP is necessary to guide therapy, the decision to catheterize should not delay the initial therapeutic steps. Prompt action should follow observation of tachypnoea, cough and agitation followed by increasing work of breathing, dyspnoea, diaphoresis, inspiratory retractions and flaring of the *alae nasi.* Further observations such as a cold, clammy and cyanotic skin, awake patients having difficulty to speak and wanting to sit upright or thrashing about, strengthen the diagnosis. Auscultation of the chest will demonstrate wheezes and rales. Arterial bloodgas analysis will indicate hypoxaemia and hypocarbia. Pink frothy sputum is produced as a result of accumulating alveolar fluid, which also contains red blood cells leaking through the distended capillary wall. Patients on mechanical ventilation support demonstrate a decrease in pulmonary compliance and an increased peak airway pressure which is necessary to deliver the tidal volume.

Immediate therapeutic goals include an attempt to:

- improve oxygenation

- reduce preload (venous return)

- reduce anxiety

- identify and manage precipitating factors vigorously.

The patient should be placed in a sitting position, with his legs down. Humidified 100% oxygen should be given - preferably by positive pressure mask. Vital signs as well as arterial and mixed venous bloodgas shoul be monitored frequently. Pulse oximetry is very

useful to monitor the saturation of arterial blood during resuscitation. An ECG and chest radiograph should be obtained as soon as possible.

Supraventricular or ventricular tachydysrhythmias should be treated. Intravenous morphine (2-10 mg every 10-15 minutes) will reduce preload and allay anxiety. Nitrates given sublingually or intravenously rather than diuretics may be the best firstline treatment for acute pulmonary oedema with elevated preload. Nitrates cause mainly vasodilatation with some arterial dilatation. This results in prompt reduction of preload with little change in cardiac output.

This redistribution of the blood volume rapidly alleviates symptoms, but it is a temporary measure and must be followed by more definite treatment.

Furosemide (20-40 mg) should be given intravenously and then repeated in increasing doses as necessary to achieve a diuresis if the patient has not yet responded. One should guard against unnecessary large doses of furosemide because excessive diuresis will result in reduction of the cardiac output.

Pulmonary oedema associated with hypotension may necessitate inotropic support - intravenous dobutamine (5-15 microg/kg/min) is the drug of choice. Digitalis is not indicated as an inotropic agent, but might be indicated to slow the ventricular rate in cases with atrial flutter or fibrillation.

Aminophylline should be avoided because of its marked positive chronotropy and arrhythmogenicity. The beneficial effects of aminophylline can be achieved more effectively and with less risk by the abovementioned drugs.

Intubation and positive pressure ventilatory support should be considered early in patients in whom oxygenation deteriorates despite aggressive treatment.

In refractory cases tourniquets applied to three of the four extremities and rotated every 15-20 minutes may be of value. Tourniquets should be inflated sufficiently to occlude venous return but not to impair arterial flow. Phlebotomy or haemodialysis could also be considered.

Prognosis

The Framingham study found that if a diagnosis of heart failure was made, death supervened within four years in 52% of men and 34% of females, regardless of the cause of heart failure. Withing five years after the first myocardial infarction 14% of men developed heart failure and 50% died within five years.

The long-term prognosis of patients with heart failure depends mostly on the degree of failure at diagnosis. Patients with a class III to IV failure have more or less 50% survival after one year and 30% survival after two years. Patients usually die a sudden death due to ventricular dysrhythmias or after progressive heart failure.

One of the most important contributing risk factors is the patient's age. Increasing age

is without doubt associated with higher mortality. The presence of hypertension is also indicative of poor prognosis and calls for aggressive treatment. In women diabetes mellitus contributes to a five-fold increase in the prevalence of heart failure as against the normal population. Men only have a twofold increase in risk. Cigarette smoking doubles the risk of heart failure in females but is not a strong determinant of heart failure in men.

The prognosis of heart failure after diagnosis mainly depends on the degree of failure. Although treatment of heart failure may control the symptoms to a large extent, it has not made a big difference to the long-term prognosis of these patients. Treatment therefore is aimed mainly at complications and symptoms at this stage. The use of combined venodilators and arterial vasodilators sucg as the ACE-Is or a combination of oral nitrates and hidralazine have, however, been shown to reduce mortality.

Part 2

Recognition and Management of Cardiac Dysrhythmias

Introduction

Precise interpretation and analysis of dysrhythmias can be a challenging exercise even to seasoned cardiologists. The practising surgeon should be familiar with:

- the principles of electrocardiography

- the diagnosis and management of basic and common dysrhythmias

- the diagnosis and management of life-threatening dysrhythmias

- the drugs and equipment needed for cardiopulmonary resuscitation

An acceptable familiarity with dysrhythmias can be achieved by a direct and simple approach to the underlying pathophysiology.

Basic Electrophysiology

The biggest part of the heart consists of muscle cells or myocytes, but it also contains specialized tissues which can generate and propagate regular electric activity. The electrical activity of the heart starts in specialized cells or pacemaker cells which are located in the sinoatrial node (SA) near the junction of the superior vena cava and right atrium. From here the electrical impulse spreads rapidly throughout the atria, along interatrial conduction fibres and the internodal pathways to reach the atrioventricular node (AV) which is situated in the lower portion of the interatrial septum near the ostium of the coronary sinus in the right atrium (fig. 3.3.8). These fibers have a very slow rate of propagation. Malfunction of the AV node can lead to heart block. The impulse is delayed at the AV node long enough to allow the atria to empty and the ventricles to fill. The impulse is then distributed very rapidly to the ventricles along the bundle of His, bundle branches, and Purkinje fibres, enabling the numerous myocytes of the ventricles to be excited almost synchronously. This allows blood to be ejected into the aorta at pressure rather than simply being moved between different parts

of the ventricular cavities as may happen, for example, during very rapid ventricular arrhythmias.

Cells in the sinoatrial node, conduction pathways, the atrioventricular node and the His-Purkinje system may all demonstrate spontaneous diastolic depolarization. Ordinarily the rate of depolarization in cells other than those found in the sinoatrial node (which has a normal spontaneous depolarization rate of 60-100 beats per minute) is so slow that automaticity in these cells is suppressed by the propagated impulse arising from the sinus node. The AV node for instance depolarizes at 40-60 beats per minute.

The ability of a myocyte to repsond to an electrical stimulus is termed excitability. The cell loses its ability to respond following depolarization and becomes refractory until repolarization has occurred again. Antiarrhythmic drugs are believed to abate arrhythmias because they increase the duration of the refractory period relative to the speed of impulse conduction.

Alterations in conductivity may produce local or general heart block. Block is particularly common in the AV node because of the slowness of conduction through that area. Two important physiologic mechanisms, the presence of refractory tissue and the phenomenon of decremental conduction, account for many of the conduction disturbances seen in the critically ill.

The typical electrocardiogram (ECG) demonstrates the normal impulse generation and conduction. The various waves of the ECG correspond to different portions of the activation cycle (fig. 3.3.8).

Interpreting the ECG

The ECG remains the most important and definitive single noninvasive diagnostic test. A 12-lead electrocardiogram with an additional long recording employing the lead with distinct P-waves is usually obtained for proper analysis.

To interpret the ECG, one must understood the dimensions of the ECG recording paper. Each square (5 mm) on the ECG paper represents 0.20 seconds, and each small square (1 mm) represents 0.04 seconds at a normal paper speed of 25 mm/sec. A one minute strip contains 300 large squares. To approximate heart rate, one should divide 300 by the number of large squares counted between two R-waves. If a more precise rate is needed, divide the number of small squares between R-waves into 1500. These methods work well if the rhythm is regular.

If the heart rate is regular, the underlying rhythm may be sinus rhythm, junctional rhythm, atrial tachycardia, atrial flutter or ventricular tachycardia, as well, as third degree AV block. If it is irregular, premature atrial beats, premature ventricular beats, atrial fibrillation, multifocal atrial rhythm or some type of second degree AV block may be present.

The following basic rules should then be applied:

A. Identify atrial activity - P waves:

- Are they normal, or ectopic origin, flutter-waves or atrial fibrillation waves and do all the P waves look the same?

- Do the atria depolarize anterograde (P positive in II) or retrograde (P negative in II).

- What is the atrial rate?

- Is the atrial rate regular?

- Are P waves inverted in leads where they should be upright?

B. Identify ventricular activity - QRS complexes:

- Is the QRS duration normal? (<0.10 sec). If not, ventricular depolarization may be initiated via abnormal conduction fibres i.e. bundle branch block, or it may be due to ventricular ectopy.

- What is the ventricular rate?

- Is the ventricular rate regular?

- Is there a P wave related to each ventricular complex?

- Does the P wave precede or follow the QRS complex? PR <0.1 or PR>0.4 usually indicates dissociation of P waves and QRS complexes.

- Are the ventricular complexes identical?

C. Determine the QRS axis:

The QRS axis indicates the direction of the mean QRS vector in the frontal plane. This can be determined by the limb leads. The normal axis in adults ranges from + 90 to - 30.

To approximate the axis the hexaxial system should be used (fig. 3.3.12). This system is based on the work of Einthoven who first described an equilateral triangle with the heart at the centre. This triangle is formed by the three standard ECG leads.

In an electrical sense, all electrodes placed at a distance greater than 15 cm from the heart may be considered to be equidistant from the heart. Using this principle, Einthoven placed the electrodes of the three standard leads as far away from the heart as possible, i.e. on the extremities - the right arm, left arm and left leg. The three standard leads derived from these electrodes are (fig. 3.3.10):

- Standard lead I: right arm (negative pole) and left arm (positive pole)

- Standard lead II: right arm (negative pole) and left leg (positive pole)

- Standard lead III: left arm (negative pole) and left leg (positive pole)

The three lead axes of the Einthoven triangle may be rearranged so that they pass through the same zero point (the heart to form a triaxial system).

The next group of leads are the unipolar limb leads. They are derived by attaching the positive pole of each lead to one of the limbs. The negative pole of each unipolar limb is attached by three wires to the other three limb electrodes. The negative pole of each unipolar lead represents the zero potential which is located at the centre of the Einthoven triangle. The axis of a unipolar limb lead represents a hypothetical line drawn from the limb, right shoulder or left hip to the centre of the Einthoven triangle (fig. 3.3.11) forming another triaxial system.

When these two triaxial systems are combined, a hexaxial reference system is formed. This system divides the frontal plane into 30 degree intervals. The six leads keep their original polarity, but by convention all degrees in the upper half of the reference system are labelled negative, and those in the lower half positive (fig. 3.3.12).

The best way to determine the axis is to find the lead with the tallest R wave. The mean QRS vector points roughly in this direction. Next look for the lead where the QRS is most isoelectric or equally biphasic. The QRS vector is approximately perpendicular to this lead. When this information is combined, the position of the axis can be estimated (table 3.3.8).

The presence of pathological features such as broad and deep Q waves indicating myocardial infarction, must be noted. Ventricular hypertrophy can be deduced from QRS voltage. The duration and morphology of the QRS complex may indicate a specific bundle branch block. Displaced ST segments are very important indicators of ischaemia. The T wave may indicate hypokalaemia if flattened or inverted whereas tall, peaked T waves indicate hyperkalaemia.

When recording an ECG and especially when monitoring a patient post-operatively, it is very important to remember that the electrodes and cables should be connected according to these principles to create an Einthoven triangle. Haphazard application of the electrodes and cables will not yield information of diagnostic quality.

Table 3.3.8. Causes of Axis Deviation

Right	Left
- Right ventricular hypertrophy	- Inferior infarction
- Switched arm electrodes	- Wolff-Parkinson-White syndrome
- Dextrocardia	- Emphysema
- Wolff-Parkinson-White syndrome	- Left anterior hemiblock
- Left posterior hemiblock	- Apical ectopic ventricular impulse
	- Apical pacemaker discharge
	- Advanced pregnancy

Classification of Dysrhythmias

Sinus rhythm originates in the sinus mode at a rate of between 60 and 100 beats per minute and is considered the normal heart rhythm. This is usually regular although respiration may cause some variation. Dysrhythmias (= arrhythmia = abnormal heart rhythm) are most often seen in patients with heart disease, but can also be manifestations of other conditions. Metabolic and electrolyte status, hypoxia or possible drug ingestion should be considered as potential precipitating causes. The clinical setting may also be important, for example, newborns are subject to premature atrial beats; hyperthyroid patients can present with episodes of supraventricular dysrhythmias and certain cardiac conditions such as atrial septal defects and Wolff-Parkinson-White (WPW) syndrome are causes of atrial dysrhythmias.

It is useful to classify dysrhythmias according to their origin. Although not comprehensive, the following classification contains the most common and important dysrhythmias.

Tachydysrhythmias

Supraventricular

- Sinus tachycardia

- Ectopic atrial tachycardia

- Atrial flutter

- Atrial fibrillation

- Paroxysmal supraventricular tachycardia

Ventricular

- Ventricular extrasystole

- Ventricular tachycardia

    - Monomorphic
    - Polymorphic (Torsade de Pointes)

- Ventricular fibrillation

Bradydysrhythmias

Atrial

- Sinus bradycardia

- Sinus arrhythmia

- Sinus arrest and SA block

- Sick sinus syndrome

AV nodal

- 1st degree block: delayed conduction

- 2nd degree block: intermittent conduction

    - Wenckebach type
    - Mobitz type II

- 3rd degree block: no AV conduction

Dangerous Dysrhythmias

Another way to approach dysrhythmias is according to their inherent danger or urgency (table 3.3.10). Dangerous dysrhythmias are disturbances of rhythm that are likely to cause haemodynamic embarassment or death and require immediate therapy. The spectrum of dangerous dysrhythmias extends from asystole and ventricular fibrillation (VF) to those dysrhythmias that have the potential for producing haemodynamic impairment or electrical catastrophe. According to Ramo "a haemodynamically significant dysrhythmia is one that is or has the potential to cause haemodynamic embarassment or increase myocardial oxygen consumption to a degree that may result in myocardial infarction (MI)". However, animal studies by Coetzee et al. suggest that ischaemia is more likely to be due to diminished coronary blood flow as a result of shortened diastolic period, implicating myocardial oxygen supply rather than consumption. A dysrhythmia is electrically significant if it causes or is likely to cause VF, asystole, or a bradycardia that may precipitate cardiopulmonary arrest.

It is important to realize that a dysrhythmia which may be benign in a patient with normal cardiac function will cause an emergency in another patient with cardiac dysfunction or a serious concomitant medical problem such as bleeding, respiratory failure or hypervolaemia. The importance of a given dysrhythmia depends therefore on whether it is or has the potential to become haemodynamically or electrically significant (table 3.3.9).

A simple classification according to urgency is:

- urgent dysrhythmias

- semi-urgent dysrhythmias

- stable dysrhythmias

- chronic dysrhythmias

Table 3.3.9. Clinical importance of cardiac arrhythmias

Clinical Presentation

Haemodynamic effects

- Impaired cerebral perfusion - Somnolence, confusion, agitation
- Impaired peripheralperfusion - Cool, diaphoretic extremities, peripheral cyanosis, acidosis
- Left ventricular failure - Pulmonary oedema, hypotension
- Increased myocardial O_2 consumption - Angina pectoris, acute MI

Electrical effects

- Asystole, severe bradycardia - Cardiac arrest, coma, confusion
- Ventricular fibrillation - Cardiac arrest

An unconscious patient with no palpable pulse should be treated immediately. The precise identification of the dysrhythmia can wait until the patient has been stabilized. Semiurgent dysrhythmias could become urgent if steps are not taken to prevent this. Stable dysrhythmias are those which have not caused haemodynamic or electrical problems, but which must be treated to prevent haemodynamic sequelae. The chronic dysrhythmias may require conversion, but there is no urgency.

The Pathogenesis of Dysrhythmis

The haemodynamic embarrassment of dysrhythmias may range from depressed cardiac output producing ischaemia in susceptible organs, to compete circulatory arrest on the other hand. This may be the result of ventricular rates that are either too slow or too fast. Ventricular rates of between 40 and 160 beats per minute are usually well tolerated as physiological adaptations, within which an adequate cardiac output and blood pressure can be maintained. Above 160 beats per minute cardiac output usually decreases. In the presence of myocardial or peripheral arterial disease, rates below 50 or above 120 beats per minute may produce ischaemia in susceptible organs.

Excitability and Conductivity

Factors affecting excitability and conductivity are:

- **Hypoxia,** which is an extremely important cause of dysrhythmias in the critically ill patient. In normal individuals hypoxia will cause adrenergic stimulation with elevation of pulse and blood pressure. This response is often weakened in critically ill patients. Bradycardia or complete inhibition of impulse formation is a particular danger of vagal stimulation in the presence of hypoxia.

- **Respiratory acidosis,** may lead to dysrhythmias in cases of sudden ventilatory failure. An acute increase in $PaCO_2$ in the previously normal patient causes a sharp decrease in pH which increases myocardial irritability. Hypercapnia and hypoxia together account for many of the fatal dysrhythmias found in the critically ill.

- **Metabolic acidosis,** is usually associated with hyperkalaemia, which may precipitate ventricular dysrhythmias. Acidosis renders the heart insensitive to the effects of catecholamines, it decreases myocardial contractility and leads to dysrhythmias which cannot be terminated by electrical countershock. If the pH is < 7.2 it is necessary to administer bicarbonate to decrease plasma potassium. Ventricular fibrillation, previously refractory to electrical conversion, may now be terminated by electrical countershock.

- **Hyperventilation** with respiratory alkalosis and hypokalaemia may also cause cardiac dysrhythmias.

Mechanisms of Tachydysrhythmias

There are basically two mechanisms responsible for cardiac tachydysrhythmias:

- an abnormality of impulse generation.

- an abnormality of impulse conduction.

An ectopic focus is a region of the heart in which acquired abnormal impulse generation takes over the pacing activity of the SA node. The ectopic pacemakers may result from enhanced activity of subsidiary pacemaker cells or an abnormal activity of cells which seldom possess spontaneous diastolic depolarization. Various drugs, ischaemia, or the effects of inflammation of the heart may produce abnormal automaticity, i.e. the various tachycardias produced by digitalis toxicity.

Re-entry occurs when a closed loop of conducting tissue transmits an electrical impulse around the loop. This can happen once or repeatedly. With each pass around the circuit an atrial or ventricular contraction is stimulated (fig. 3.3.13).

These re-entry loops can be due to an anatomical obstacle in the conduction system, or a functional electrophysiological difference between adjacent regions of heart muscle.

Mechanisms of Bradydysrhythmias

Bradydysrhythmias are also caused by two mechanisms, namely:

- Depression of the dominant pacemaker - normally the SA node.

- Conduction system blocks.

In both situations, subsidiary pacemakers take over to pace the heart. The rate is usually slower than the sinus node.

Recognition and Management of Specific Dysrhythmias

The therapeutic approach to a patient suffering from a cardiac dysrhythmia begins with an accurate electrocardiographic interpretation of the dysrhythmia provided there is no clinical emergency (table 3.3.10). The cause of the dysrhythmia should be determined next, if

possible. This is followed by a search for underlying heart disease and an evaluation of the consequences of the dysrhythmia in the individual patient. Knowledge of the entire clinical situation is essential before one can start treating dysrhythmias.

An important concept to keep in mind is that ECG diagnosis rests on analyzing the sequence and relationship of both atrial and ventricular activity. Atrial activity may be difficult to interpret, particularly with a tachycardia in which P-waves may not be visualized on the ECG. Carotid sinus massage is a useful technique to bring out ECG signs of atrial activity in supraventricular tachydysrhythmias, such as atrial flutter, because it slows AV conduction and can increase the AV block in atrial flutter from 2:1 to 3:1 or 4:1, thus making P-waves visible on the surface ECG.

The four basic principles of antidysrhythmic therapy are (table 3.3.11):

- Inhibition of the fast sodium channels by quinidine or lidocaine or related compounds.

- Beta-adrenergic receptor antagonism.

- Inhibition of repolarization.

- Inhibition of the slow calcium channel in the atrioventricular node.

In each patient the potential benefit to be achieved must be balanced against the possible side effects before starting treatment, because antidysrhythmic drugs may induce or exacerbate dysrhythmia *per se.* Many of these agents are used to treat patients with potentially life-threatening ventricular tachydysrhythmias in the presence of serious underlying heart disease. This potential for prodysrhythmic effects is therefore of great clinical concern.

One must bear in mind that if a drug of one group is unsuccessful, it is unlikely for another molecule from the same group to have a beneficial effect.

Table 3.3.11: Classification of Antidysrhythmic Drugs

Class I. Sodium ("fast") channel blockers, slow depolarization:

IA: Moderate slowing of depolarization and conduction, prolongs repolarization and action potential duration.

Quinidine.

Procainamide.

Disopyramide.

Ib: Minimal slowing of depolarization and conduction, tends to shorten repolarization and action potential duration.

Lidocaine.

Phenytoin.

Mexiletine.

IC: Marked slowing of depolarization and conduction, tends to prolong repolarization and action potential duration.

Flecainamide.

Encainamide.

Class II. Beta-adrenergic antagonists.

Propranolol.

Esmolol.

Class III. Prolong action potential and refractory period duration, antifibrillatory activity.

Bretylium.

Amiodarone.

Sotalol.

Class IV. Calcium ("slow") channel blockers.

Verapamil.

Diltiazem.

Supraventricular Tachydysrhythmias

Sinus Tachycardia

Any sinus rhythm faster than 100 beats per minute is regarded as a sinus tachycardia. It is seldom faster than 150 beats per minute and is always secondary to conditions such as fear, shock, anaemia, fever, hyperthyroidism, heart failure, etc. Any condition associated with an increased sympathetic output will cause sinus tachycardia.

- **ECG:** Normal P waves, PR time and QRS complexes are present. Only the heart rate is increased.

- **Importance:** The tachycardia *per se* has no diagnostic or prognostic ßÑ n, but the underlying condition must be treated. In anxious patients beta-blockers are useful provided

no underlying disease is present. Hyperthyroidism may present with tachycardia especially in elderly patients, before the other clinical signs of hyperthyroidism become obvious. Patients with diminished left ventricular reserve often develop sinus tachycardia as the earliest sign of impending heart failure. Sinus tachycardia is also one of the early indicators of hypovolaemia.

Atrial Extrasystoles

Atrial extrasystoles originate from cells of the left or right atrium and are usually of no haemodynamic importance. Multiple atrial extrasystoles may be an indication of impending atrial fibrillation. This occurs usually in patients with underlying heart failure or valvular lesions with haemodynamic significance. Anxiety, cardiac stimulants (bronchodilators, digitalis, beta-adrenergic antagonists), excessive consumption of coffee and alcohol as well as cigarette smoking may also give rise to atrial extrasystoles.

Diagnosis

- On clinical examination only the irregular pulse can be found. No compensatory pause is present.

- An ECG provides the only way to diagnose this condition with certainty. A normal QRS complex is preceded by a P wave which depolarises earlier than normal and has an abnormal configuration. An important characteristic is the fact that the QRS configuration cannot be distinguished from the normal sinus beats.

Management

- Most cases do not need any treatment.

- Precipitating causes must be eliminated.

- Low dose beta-blocker may be indicated for anxious patients.

Ectopic Atrial Tachycardia

This rare dysrhythmia must be distinguished from the other atrial tachydysrhythmias, especially sinus tachycardia. Two types of this dysrhythmia have been distinguished electrophysiologically - **automatic** and **re-entrant atrial tachycardia.** The latter rarely ocurs and will not be discussed.

Automatic Ectopic Atrial Tachycardia

The electrocardiographic features of this condition are characterised by a supraventricular tachycardia that generally accelerates gradually after its initiation, with heart rates less than 200 beats per minute.

The P wave differs from the sinus P wave, the PR interval is influenced directly by the site of the ectopic focus and the rate of the tachycardia and AV block may exist without

affecting the tachycardia.

This condition can occur in all age groups. Causes may be:

- digitalis toxicity

- myocardial infarction

- chronic lung disease with acute infection

- acute alcohol ingestion

- various metabolic derangements.

Management is difficult because this dysrhythmia is usually resistant to drug therapy. Vagal manoeuvres generally do not terminate the tachycardia even though they may cause AV nodal block, with a decrease in the ventricular rate. Electrical cardioversion is usually also unsuccessful. If digitalis toxicity is present, this should be treated. The class Ia antidysrhythmic drugs, quinidine sulphate, disopiramide and procainamide are usually most effective. Verapamil is not effective although it may slow the conduction through the AV node.

Atrial Flutter and Atrial Fibrillation

These atrial dysrhythmias are closely related are closely related and will be discussed together. In practice atrial fibrillation is certainly one of the most common atrial dysrhythmias. It may be secondary to several diseases and is always pathological. Both these dysrhythmias develop probably because of atrial re-entry. Atrial flutter (atrial rate of 250-350 beats per minute) tends to be unstable and may revert to sinus rhythm or degenerate into atrial fibrillation. This may be because the atrial flutter has a micro re-entry circuit as focus of the dysrhythmia. The depolarization front spreads from there in a centrifugal pattern through the rest of the atria. If the atrial tissue has inhomogenous refractory properties the depolarization wave will be fragmented into multiple small wave fronts which then cause the multiple atrial-fibrillation waves.

The atrial discharge rate during fibrillation is 500-600 beats per minute. A significantly slower ventricular rate is present due to conduction delay in the AV node, but it is also totally irregular and usually occurs at a rate of between 100 and 160 beats per minute. In patients with untreated atrial flutter the ventricular rate is usually half the atrial rate, i.e. 150 beats per minute due to 2:1 AV block. In some conditions atrial flutter may conduct to the ventricular rate of 300 beats per minute. A high degree AV block may also be present, allowing only every third or fourth impulse to pass to the ventricle. The ventricular rate and rhythm thus depend on the number of impulses conducted through the AV node.

Because of the total electrical reigning in the atria during atrial fibrillation, there is no orderly impulse conduction and consequently also no effective atrial contraction. The loss of the atrial contribution (± 25%) to ventricular filling may cause the cardiac output to drop significantly in patients with heart failure, mitral stenosis, aortic stenosis, hypertrophic

cardiomyopathy and ischaemic heart disease. Patients with mitral stenosis may develop acute increase in left atrial pressures and pulmonary oedema when fast atrial fibrillation sets in.

Aetiology

1. Valvular disease

- Mitral stenosis or incompetence

- Mitral valve prolapse

- Aortic stenosis

2. Myocardial involvement

- Chronic ischaemic heart disease

- Myocardial infarction with concomitant atrial infarction or heart failure

- Congestive and hypertrophic cardiomyopathy

3. Involvement of the pericardium by pericarditis or after cardiac surgery

4. Systemic hypertension

5. Hyperthyroidism

6. Pulmonary disease

- Chronic obstructive-airways disease

- Pulmonary embolism

7. Drugs

- Excessive alcohol consumption

- Digitalis toxicity

- Electrolyte disturbances - hypokalaemia and/or hypomagnesaemia

- High level of circulating catecholamines.

Complications

Haemodynamic

- Decreased cardiac output, especially when the ventricular response is very fast

- Increased oxygen consumption and/or decreased oxygen delivery, causing exacerbation of ischaemia in patients with ischaemic heart disease.

Embolic

35% of patients with atrial fibrillation will embolize at some stage. Anti-coagulants are therefore indicated.

Risk factors for embolization:

- Atrial fibrillation *per se*

- Large left atrium (> 50 mm on echocardiography)

- History of previous embolus

Patients on Warfarin therapy are at risk for:

- Cerebral haemorrhage - 1% per year

- Non-cerebral haemorrhage - an additional 2% per year. Antiplatelet agents carry less risk but may not be as effective to prevent embolization.

Symptoms

- Patients may be asymptomatic, but are mostly aware of the irregular heart beat.

- Atrial fibrillation may be chronic or intermittent. If intermittent, the sudden drop in cardiac output may often lead to diminished cerebral blood flow with dizziness, vertigo and even syncope.

- In patients with mitral stenosis the onset of fast AF is associated with pulmonary congestion and even acute pulmonary oedema. Patients who were relatively asymptomatic previously, will develop symptoms now.

- Chronic AF may present with systemic embolization as the first manifestation. The embolus may occlude a cerebral, renal, mesenteric or even a limb vessel.

Diagnosis

- This dysrhythmia (atrial fibrillation) is characterized by a totally irregular heart rhythm. Very fast or slow rates may obscure the irregularity.

- The a-wave of the pulsations in the neck veins will be absent because of the absence of effective atrial contractions.

- Often with fast ventricular rates a significant pulse deficit appears, during which the apical rate is faster than the rate palpated at the wrist because each contraction is not strong enough to open the aortic valve or to transmit an arterial pressure wave through the peripheral artery.

- The K1 will vary as the left ventricular volume varies from beat to beat.

- The outstanding electrocardiographic characteristic of AF is the absence of normal P waves and the presence of small irregular fibrillation waves. The QRS complexes are normal but the RR intervals vary continually. The ECG has an irregular baseline of variable amplitude and morphology, called F waves, at a rate of 350-600 beats per minute. In patients with chronic AF the amplitude of the F wave is small but in AF of recent onset F waves are bigger and coarser. AF may alternate with atrial flutter which can be seen as episodes of fast, regular, abnormal flutter waves at a rate of more or less 300 beats per minute. The atrial flutter waves have a typical sawtooth appearance on the ECG. The ventricular responses in AF is grossly irregular ("irregularly irregular"), and in the untreated patient with normal AV conduction, is usually between 100 and 160 beats per minute. Atrial fibrillation should be suspected when the ECG shows supraventricular complexes at an irregular rhythm and no obvious P waves.

Treatment

- The cause of atrial fibrillation or flutter must always be determined and corrected if possible.

- Patients who suffer acute cardiovascular decompensation secondary to fast atrial fibrillation or flutter need immediate electrical cardioversion. The treatment of atrial fibrillation as well as atrial flutter is based on the following two principles:

- **Regulate the ventricular rate:** This may be attempted by administering drugs which delay AV nodal conduction. By allowing fewer atrial impulses to pass through the AV node, the ventricular rate may be reduced to less than 100 beats per minute. This will result in an improvement of cardiac output and myocardial oxygen delivery and consumption. Metoprolol, a short acting beta-blocker for IV administration, is suitable for this purpose. The dose is 5-15 mg IV, administered at 0.5 mg/minute. Contra-indications to beta-blockers should be kept in mind.

Other drugs which may be used are:

Digitalis: 0.5 mg IV followed by 0.25 mg over the next 30 to 45 minutes may be effective. The maximum effect will occur after more or less 30 minutes so that a second dose of 0.25 mg can be given after 30 to 60 minutes. Not more than 1.0-1.5 mg should be given during the first 18 hours.

Verapamil: 2.5-10 mg should be injected intravenously over 10-20 minutes. The

negative inotropic and peripheral vasodilatory effects of this drug may cause hypotension. If necessary, additional doses of 1.5-5 mg may be repeated hourly to keep the ventricular rate under control.

- **Restore the rhythm:** When the ventricular rate is under control an attempt should be made to restore the rhythm, using medical or electrical cardioversion. Electrical cardioversion is the treatment of choice when fast atrial flutter or fibrillation results in acute cardiovascular decompensation. Electrical cardioversion should be ECG-synchronized whenever possible. Adequate sedation beforehand is necessary. The first shock should be delivered at 100 J, followed by consecutive shocks of 200 J and then 360 J if necessary. If a patient does not respond, but reverts to the original dysrhythmia, one should look for hypoxia, acidosis and electrolyte disturbances. Once these aggravating factors are corrected, cardioversion might be successful. In some patients a class Ia drug such as procainamide (50 mg/min up to a maximum of one gram) may prevent recurrence.

Medical cardioversion with quinidine or procainamide is indicated for haemodynamically stable patients. Quinidine, given with digitalis, is often necessary to convert to sinus rhythm. The dosage for quinidine sulphate is 200-600 mg every 6 to 8 hours. If this has not been successful after a few days, electrical cardioversion should be attempted.

Most investigators feel that anticoagulation prior to drug or electrical cardioversion is indicated in patients with a high risk of emboli.

Paroxysmal Supraventricular Tachycardia (PSVT)

This supraventricular tachydysrhythmia is also known as paroxysmal atrial tachycardia (PAT). It is usually the result of re-entry of impulses within the AV node. The re-entry circuit may be situated at the level of the AV node, or an accessory circuit may be involved, in which case it is called atrio-ventricular re-entry.

The electrocardiographic characteristics of this dysrhythmia include a tachycardia with narrow complexes at a rate of 150-250 beats per minute. Because of the fact that the re-entry circuit initiates retrograde depolarization process in the atria and ventricles occur simultaneously. As a result the P waves fall inside the QRS complexes and may be difficult to identify. Usually, the ventricules are depolarized via the normal conduction fibres, producing normal QRS complexes, but pre-existing bundle branch block or aberrant conduction will prolong the QRS complexes.

Since the AV node is always part of the re-entry circuit, drugs with slow conduction through the AV node are highly effective in treating this dysrhythmia. The drug of choice is verapamil. Beta-blockers, digitalis or class Ia drugs may be used as well. Patients with fast PSVT may also develop cardiovascular decompensation in which case electrical cardioversion is indicated.

Ventricular Tachydysrhythmias

The prognosis of this group of dysrhythmias is variable, and the spectrum of these conditions extends from single unifocal ectopic ventricular contractions to fatal ventricular

fibrillation. Ventricular tachycardia usually preceeds fibrillation. Certain ectopic ventricular beats are also inclined to degenerate to ventricular tachycardia.

Ventricular Extrasystoles (VES)

A synonym for VES is premature ventricular complex (PVC). A ventricular extrasystole is an irregular early interruption in the normal rhythm, and originates from an ectopic focus in the ventricle which discharges prematurely. The VES is premature because it arises in the diastolic phase of the preceding sinus beat, giving rise to a bizarre QRS complex which is recorded earlier than the next anticipated sinus beat.

Mechanism

The ectopic beats may arise in either the left or the right ventricle. The usual origin are the Purkinje fibres but may also be myocardial cells. The mechanism may be based on increased automaticity, re-entry or triggered activity. Although an underlying cause can usually be found, it may be impossible to demonstrate any aetiological factor.

The ectopic impulse is not conducted through the normal conduction system, but via the muscle tissue. For this reason depolarization is slower than normal and the QRS complex prolonged. The morphology of such an ectopic beat is also different from the normal sinus beat. Since there is no preceding atrial contraction, ventricular filling is suboptimal and the stroke volume less than normal.

Retrograde transmission to the atria from the ventricular extrasystole occurs fairly frequently. A P wave may then be seen in the ST segment or the T wave of the ventricular complex. In some cases this retrograde conduction of the P wave may cause symptoms such as syncope. The period between the ectopic beat and the next normal sinus beat is usually longer than those between normal sinus beats. The RR interval between the two normal QRS complexes on either side of the ectopic complex is usually twice the normally conducted RR interval. This increased RR interval is called the compensatory pause.

Clinical Features

Most patients with VES experience no symptoms. Patients may notice a feeling of discomfort in the neck or chest because of the greater than normal contraction of the postextrasystolic beat. They may also experience the sensation that the heart rate has stopped during the compensatory pause. When ventricular extrasystoles increase in frequency, patients may experience fatigue, palpitations, dizziness, syncope, or chest pain. Multiple extrasystoles may be the cause of refractory heart failure. On the other hand, poorly controlled heart failure may precipitate VES. Digitalis toxicity must always be considered when a patient treated with digoxin suddenly develops an increase in extrasystoles.

As an isolated finding in young people without underlying heart disease, ventricular extrasystoles are usually of no significance. In a young person one must always search for:

- Mitral valve prolaps

- Cardiomyopathies

- Increased QT intervals.

Ventricular extrasystoles with the following characteristics have prognostic implications:

- Multifocal VES

- Pulsus bigeminus, which refers to pairs of complexes consisting of a normal beat followed by an ectopic beat.

- Pairs or couplets, which refers to two successive ectopic complexes.

- Ventricular tachycardia which refers to three or more VES occurring at a rate of more than 120 beats per minute.

- R on T phenomenon - here the VES follows the T wave of the preceding sinus beat and can precipitate ventricular fibrillation provided it occurs within a specific critical period.

Lown has suggested the following classification as an alternative:

- Class O: no VES

- Class 1: < 30 unifocal VES/hour

- Class 2: > 30 unifocal VES/hour

- Class 3: multifocal VES

- Class 4a: paired VES

- Class 4b: three or more VES, i.e. ventricular tachycardia

- Class 5: R on T phenomenon

Classes 4b and 5 are of prognostic importance, but controversy exists about the real significance of this classification. Empirical therapy of asymptomatic VES may worsen the patient's prognosis. One reason for this is the proarrhythmogenicity of the antiarrhythmic drugs.

Diagnosis

Clinical Diagnosis

Single VES or VES that is not really earlier than normal, can be very difficult to identify clinically. If they do occur earlier than normal, the compensatory pause may be diagnostic. The absence of a compensatory pause after a premature beat, does not eliminate

the ventricular origin of the beat.

The first heart sound (K1) of the VES is softer than normal and the stroke volume is diminished resulting in a decrease in the pulse pressure. The earlier the beat the smaller the pulse pressure will be and, if very early, nothing may be palpable. In a patient with bigeminy it may seem as if the patient has a severe bradycardia because the pulse of the VES is not palpable at all.

Electrocardiographic Features

Morphologically the QRS complex of the VES obviously differs from the normal QRS complex. If arising from the right ventricle, it is usually negative in V1, and positive in V6 while the pattern of VES arising from the left ventricle is exactly the opposite. The complexes are wider than normal - usually more than 0.14 sec.

Preceding P waves are absent. Sometimes a VES occurs almost simultaneously with a normal QRS complex. Because the ventricles are then partly depolarized through the normal conduction system, the morphology is closer to that of a normal sinus beat. This is called a fusion beat. In this case it is preceded by a P wave. More often a P wave is present in the ST segment or T wave of the VES due to retrograde conduction. The ST segment and T wave of the VES are always abnormal and cannot be used to diagnose ischaemia, electrolyte disturbances or other conditions associated with ST-T wave abnormalities. A routine ECG indicates dysrhythmias over a period of 3-5 minutes at the most. The absence of VES during this period is of little value. Monitoring the ECG over a period of 24-48 hours with the aid of a portable recorder is invaluable to obtain information about the number and type of VES as well as the association between VES and symptoms. It may be used to confirm VES and also to evaluate the effect of antidysrhythmic drugs. Certain dysrhythmias are associated with exercise. A stress test can be done to elicit such a dysrhythmia. It is not clear what the relationship between VES and exercise signifies.

Treatment

Often, general measures such as elimination of stimulants (coffee, tea and nicotine) or mild sedation and reassurance, are enough to alleviate a patient's symptoms.

Underlying disease (ischaemia, heart failure, cardiomyopathy, valvular lesions, hypertension) and aggravating factors (hypoxaemia, hypokalaemia and other electrolyte disturbances, drugs) must be searched for and corrected or treated as indicated. Only after all complicating factors have been treated, should medication with antidysrhythmic drugs be considered. In some cases the dysrhythmia is serious and justifies definitive medication even when underlying disturbances have not been corrected completely. Drugs indicated to treat ventricular ectopy include:

- Lignocaine: 50-100 mg IV (1 mg/kg) as a bolus which can be repeated after 5-10 minutes if necessary. The maintenance dose is 1-4 mg per minute.

- Mexilitine: 100-200 mg 8 hourly.

- Beta-blockers: Dysrhythmias due to excessive sympathetic stimulation (i.e. hyperthyroidism and phaemochromocytoma) should respond well to propranolol 0.1 mg/kg IV as a slow infusion and a subsequent dose of 10-80 mg every 8 hours. Sotalol is a beta-blocker which also possesses class III antidysrhythmic properties which may be of value.

- Quinidine sulphate: 200-400 mg orally every 6-8 hours.

- Procainamide: 500-1000 mg IV at a rate of 50 mg per minute, followed by 250-500 mg every 4-6 hours.

- Disopiramide: 2 mg/kg IV as a loading dose and then 200-400 mg every 6-8 hours as maintenance.

- Amiodarone may be used when all the other drugs have failed.

Ventricular tachycardia (VT) is defined as a run of 3 or more VES and is considered non-sustained if it terminates spontaneously in less than 30 seconds. Ventricular tachycardia is always an abnormal rhythm. It may present as a monomorphic (uniform QRS complexes) ventricular tachycardia which is the most common type, or a polimorphic (QRS complexes vary in a random fashion) type which will be discussed later. The heart rate usually varies between 140 and 180 beats per minute. This dysrhythmia is particularly dangerous because it may degenerate to ventricular fibrillation if not treated timeously.

Ventricular tachycardia may develop in the following conditions:

- Ischaemic heart disease and left ventricular aneurysm.

- Electrolyte disturbances and hypoxaemia.

- Cardiomyopathies.

- Valvular disease, i.e. mitral valve prolapse.

- Digitalis toxicity.

- Heart catheterization.

- Coronary spasm.

Clinical Features

Patients may be surprisingly free of symptoms especially in nonsustained VT. Although sustained VT may also present with few symptoms, most often these patients are hypotensive with clinical signs of cardiogenic shock. This dysrhythmia may precipitate angina, but can also be caused by ischaemia or acute infarction. Except for the tachycardia usually associated with hypotension this dysrhythmia has no characteristic features for recognition. The diagnosis is usually confirmed electrocardiographically.

Electrocardiographic Features

It may be very difficult to distinguish ventricular tachycardia (VT) from supraventricular tachycardia (SVT) with aberrant conduction which also produces a wide complex tachycardia. A dysrhythmia with the following features is more likely to be a VT than a SVT with abberation:

- QRS complex wider than 0.14 seconds

- Left axis deviation

- AV dissociation

- Fusion beats

- Monophasic R wave or a biphasic complex in V1 with sa qR or a RS pattern

- qR or QS pattern in V6

- A QRS complex which remains the same throughout V1 to V6, i.e. all complexes remain either negative or positive.

In contradistinction a supraventricular tachycardia often exhibits:

- A triphasic complex in V1 to V6, and particularly a q in standard lead I and V6

- A rate fater than 170 beats per minute

- A QRS complex of 0.12-0.14 seconds

- The presence of pre-excitation

- A normal axis.

When it is impossible to differentiate between VT and SVT the answer may be provided by using an oesophageal electrode to trace atrial activity. If AV dissociation can be confirmed, the diagnosis of VT can be made.

Treatment

Acute therapeutic interventions should depend on the patient's clinical condition. If the patient is haemodynamically stable, medical management is in order. On the other hand, if the patient shows signs of cardiovascular decompensation, electrical cardioversion is indicated.

- Successful electrical cardioversion should be followed by antidyrhythmic medication, which normally includes lignocaine. If lignocaine is ineffective, procainamide or even disopiramide may be given. Bretilium may be used in resistant cases. Amiodarone is a relatively new drug which holds promise for the future. Unfortunately it is not immediately

effective and cannot be used in acute situations.

- Haemodynamically stable patients may be treated with lignocaine but if the VT still persists after 20 minutes, electrical cardioversion is indicated. Other drugs such as procainamide and disopiramide may be used but may cause hypotension

- In selected patients, surgery may be indicated for conditions such as ventricular aneurism. Aneurysmectomy may sometimes cure the dysrhythmia completely. Endocardial mapping may be done to localise the exact source of the dysrhythmia. Excision of diathermy of this area may be followed by permanent cure. Unfortunately very few patients qualify for surgical intervention.

Prognosis

Because of the inherent danger of degeneration to ventricular fibrillation, VT is always considered as a serious condition. It may be subdivided into a group with sustained VT (≥ 30 sec) and a group with nonsustained VT which stops spontaneously within 30 seconds. The former group has a poor prognosis while the latter grou is especially important in patients with ischaemic heart disease and diminished left ventricular function.

In the presence of acute ischaemia it may present as a transient electrical instability and is of relatively little prognostic importance. However, if it appears in a later phase of an acute infarction (after 2-3 days) the prognosis is worse. In patients with heart failure, regardless of aetiology, this dyrhythmia indicates a poor prognosis. If patients with mild cardiac disease develop nonsustained VT during exercise it is of uncertain prognostic importance, but in this group of patients it is important to exclude aortic stenosis, hypertrophic obstructive cardiomyopathy, mitral valve prolapse, and ischaemic heart disease. If any of these diseases are present, the development of VT might indicate that the patient is deteriorating. In healthy people, VT secondary to exercise may be controlled adequately with beta-blockers. Syncope and related symptoms may also be an indication of the severity of the patient's condition and these patients need treatment. These patients often suffer from episodes of prolonged or sustained VT.

Polymorphic Ventricular Tachycardia (Torsades des Pointes)

This is a special type of VT which occurs secondary to increased QT time. As the name indicates, the QRS morphology varies and usually is a cyclical change in the QRS polarity from positive to negative or vice versa. It is important to realise that this type of VT is usually associated with a definite and often treatable underlying condition. The most common causes of a prolonged QT time associated with polymorphic VT are:

- Class Ia and class III antidysrhythmic drugs

- Electrolyte disturbances (hypokalaemia, hypomagnesaemia)

- Drugs such as phenothiazine and tricyclic antidepressants

- Intracranial pathology, i.e. subarachnoid haemorrhage

- Congenital long QT syndromes

The polymorphic VT will recur continually until the cause is removed. It may also degenerate into ventricular fibrillation. In cases of unknown origin or in which the cause cannot be treated, intravenous magnesium is indicated empirically.

Class Ia and III antidysrhythmic drugs should be avoided. Class Ib drugs, i.e. lignocaine, may be effective.

Temporary transvenous atrial pacing at a rate of 100-110/minute may prevent polymorphic VT while the underlying cause is being treated. A temporary pacing electrode is advanced to the right atrial appendage. The external pulse generator is then set at 100-110 beats per minute and an output of 5 Volt. The procedure is especially helpful in cases of polymorphic VT which is aggravated by an underlying slow heart rate.

Ventricular Fibrillation (VF) (fig. 3.3.20)

This is the most serious of all dysrhythmias because of its uniformly fatal outcome if it is not treated timeously. This dysrhythmia cannot revert spontaneously and will cause death withn 3-5 minutes.

Clinical Features

VF is often the cause of sudden death. On examination the patient has no pulse or respiration or blood pressure. Clinically the patients eems to be dead and there are no characteristics to distinguish between VF and asystole.

Electrocardiographic Features

VF is recognized by the presence of a totally irregular undulating pattern of varying contour and amplitude. No P or QRS can be identified.

Treatment

Immediate Cardiopulmonary Resuscitation

Specific Treatment

- Electrical cardioversion: A sharp blow with a closed fist on the precordium may help to revert the VF. Cardiopulmonary resuscitation (CPR) according to the principles of basi life support should be started immediately but employed only until defibrillation equipment is readied. Time should not be wasted with CPR if electrical defibrillation can be done immediately. Nonsynchronized DC electrical shock using 200-400 J should be applied as soon as possible. It can be repeated once or twice. If the fibrillation waves are small or fine, IV epinephrine may make them coarses and this may help to facilitate resuscitation. The sooner cardioversion is achieved the better the patient's chances for survival.

- Adequate oxygenation and ventilation is essential during resuscitation. Frequent

blood-gas analysis and pH determinations are necessary. Metabolic acidosis should be treated with sodium bicarbonate if the pH is less than 7.2 (see chapter on acid-base metabolism).

- As soon as an acceptable rhythm is achieved a bolus dose of lignocaine at 1 mg/kg should be administered IV. The maintenance dose is 2-4 mg/min.

- In refractory cases bretilium 5 mg/kg should be given IV over 10 minutes. This should be followed by a maintenance dose of 1-2 mg/min.

- It is very important to establish and correct the cause of VF in all cases. Blood-gas analysis and serum electrolyte determinations must be done to exclude hypoxia and electrolyte disturbances. As soon as an acceptable rhythm is established, myocardisal infarction must also be excluded. Rare causes such as the long QT syndrome or cardiomyopathies must be kept in mind.

Bradydysrhythmias

Dysrhythmias and disturbances of conduction should not be confused. The former condition refers to the development of an abnormal cardiac depolarization wave in normal or abnormal tissue, within or outside the normal conduction system. Disturbances of conduction refer to diseases which interfere with the normal conduction of a cardiac impulse. Because these conditions may overlap, both conditions may be present simultaneously in the same patient. Disturbances of conduction may develop in the SA node, the AV node, the bundle of His or the bundle branches. According to Zipes, Heart block is a disturbance of impulse conduction that may be permanent or transient, owing to anatomical or functional impairment".

Sinus Bradycardia

A pulse rate of less than 50 beats per minute is defined as bradycardia. If the impulse originates in the SA node, it is called a sinus bradycardia. It is important to distinguish this condition from other causes of bradycardia, i.e. heart block.

Sinus bradycardia may be associated with the following situations:

- Physical fitness.

- Sleep.

- Drugs, particularly beta-blockers, calcium-channel antagonists, alphamethyldopa, digitalis, reserpine, etc.

- Hypothyroidism.

- Obstructive jaundice.

- Increased intracranial pressure.

- Sick-sinus syndrome.

Diagnosis

On clinical examination the patient will have a regular, slow heart rate. A mild systolic hypertension may be present, and sometimes a systolic ejection murmur over the aortic valve. The ECG will show normal P waves followed by normal QRS complexes.

Importance

Patients with sinus bradycardia are normally asymptomatic. When symptoms such as dizziness, syncope, fatigue or heart failure develop, further investigation is indicated. Drugs which may be involved, should be discontinued. If this is impossible, placement of a permanent pacemaker should be considered. This is also necessary when the cause of the bradycardia cannot be treated, i.e. sick-sinus syndrome.

Sinus Arrhythmia (fig. 3.3.21)

Normally, the heart rate will increase slightly with inspiration and decrease again with expiration. This normal variation in heart rate is more pronounced in children and young people. Patients with sinus arrhythmia are asymptomatic and this phenomenon should be noted to avoid confusion with dysrhythmias. The diagnosis canbe made by examining the relationship between the heart rate and respiration. If the clinical diagnosis is difficult, it can be demonstrated electrocardiographically by asking the patient to breath slowly and deeply while a rhythm strip is being recorded. The phasic acceleration with inspiration and decelleration with expiration will be shown. This condition requires no treatment and is proof that the autonomic nerve supply to the heart is intact.

Sinus Arrest and SA Block

SA Block

When the impulse transmitted by the P cells of the SA node does not reach the atrium, SA block is present. The impulses from the SA node are intermittently being blocked totally. On the ECG it can be recognized as intermittent pauses which have exactly twice the duration of the usual PP time, or multiples thereof.

Sinus Arrest (Fig. 3.3.22)

In this condition no impulses are generated in the SA node and no P waves can therefore be found on the ECG. After a pause an escape rhythm of the second fastest pacemaker outside the SA node usually takes over the pacemaker function. Usually this will be the AV node or another atrial focus.

Aetiology of SA Block

Vagus stimulation is the most common cause. Very fit individuals usually have a degree of vagal domination and may exhibit some of these dysrhythmias. Drugs causing SA

block include digitalis, beta-blockers, verapamil and lithium preparations. Patients with inferior myocardial infarction may experience transient episodes of SA block or degrees thereof.

Treatment

If symptomatic, the patient should receive an atrial pacemaker. Normal conduction through the AV node should be established first as a ventricular pacemaker will be necessary otherwise. Electrophysiological studies can determine the status of AV conduction. A number of these patients will probably develop AV conduction disturbances at a later stage, despite normal test initially.

Atrioventricular Block

The most common conduction disturbance found in clinical practice is atrioventricular conduction block. It is more prevalent than SA block and can be diagnosed readily. This conduction disturbance is classified by severity into three categories.

First-Degree Heart Block (fig. 3.3. 23)

This condition has no particular clinical characteristics. The K1 may be softer than normal in some cases. A constantly prolonged PR interval (> 0.20 sec) is the characteristic ECG finding. Every atrial impulse is conducted to the ventricle and every P wave is followed by a QRS complex - only the PR intervals are prolonged.

First-degree heart block may be caused by:

- Vagus stimulation.

- Drugs, i.e. digoxin, verapamil, beta-blockers as well as some of the other antidysrhythmic agents.

- Myocarditis.

Second-Degree Heart Block (fig. 3.3.24)

Second-degree heart block occurs in two forms: Mobity type I, also termed the *Wenckebach phenomenon,* and Mobity type II.

Mobity Type I AV Block

In this case the AV node itself is affected, either temporarily or permanently. A Wenckebach phenomenon will develop in most normal individuals when the heart rate is increased to more than 140 beats per minute during atrial pacing. This does not happen during exercise because sympathetic stimulation is present as well. Patients are asymptomatic as a rule.

The ECG will show progressively lengthening of the PR interval until an impulse is

not conducted and a QRS complex falls away. This cycle will then restart and repeat itself continually.

This condition has a good prognosis and does not need treatment.

Mobity Type II AV Block

In this case the pathology is situated in the AV node or the bundle of his, distal to the AV node. This implies that the distal escape pacemaker is situated in the Purkinje fibres which can discharge at a rate of 20-40 beats per minute only. Type II block is a more serious condition which tends to degenerate into third-degree AV block.

Clinical Features

The diagnosis is made on the ECG which shows that the impulse is blocked intermittently in the AV node. This may occur haphazardly or at constant intervals, i.e. 2:1 or 4:1 AV block. Patients may be completely asymptomatic, but very often they complain of attacks of dizziness or syncope. These symptoms may be an indication that the patient is already experiencing third-degree AV block intermittently. They should be investigated for placement of a permanent pacemaker.

In the long-term, prognosis is determined by the underlying disease and not the heart block. Patients with an acute inferior myocardial infarction will have a good prognosis in comparison with patients who suffered anteroseptal infarctions.

Treatment

Type II block may be temporary or permanent. The temporary type always justifies a temporary pacemaker electrode connected to a pacemaker set in the demand mode if it occurs in a 2:1 fashion. Usually the conduction problem improves within days and the electrode can be removed. Patients with the temporary type usually have electrolyte disturbances or acute ischaemic heart disease.

The patient with a permanent type II AV block may require a permanent pacemaker. This is essential when the patient complains of syncope, dizziness, etc. Asymptomatic patients present a therapeutic dilemma and should be evaluated individually.

This conduction disturbance often degenerates into total AV block. The patient's symptoms should be monitored carefully if the diagnosis is not to be missed.

Third-Degree Heart Block (fig. 3.3.25)

Synonyms for the conduction disturbance are *total AV block or total AV dissociation.*

The lesion in the conduction system may again be in the AV mode or distal to the AV node. It may be located in the bundle of His or more distally in the conduction system. It may be diagnosed as a temporary disturbance during acute ischaemic heart disease, but more often it is a permanent condition. The SA node is functioning normally, but has no bearing on the

ventricular rhythm.

Proximal heart block refers to those lesions which are in the bundle of His, but proximal to the bifurcation into left and right bundle branches. In general, third-degree heart block is caused by:

- Degenerative disease of the conduction system.

- Acute and chronic ischaemic heart disease.

- Drugs - especially digoxin toxicity.

It is also sometimes associated with:

- Aortic stenosis.

- Myocarditis.

- Electrolyte disturbances.

- Connective tissue diseases.

- Congenital conditions.

Clinical Features

Onset may be acute after acute myocardial infarction. Patients who develop a total AV block after an inferior infarction usually have a good prognosis and the block normally improves within five days. On the other hand, patients with total AV block secondary to anterior infarction have a poorer prognosis due to the extent of the lesion.

Some patients suffer from chronic third-degree heart block. In these cases the time of onset is unknown. The symptoms and signs may include:

- Stokes-Adams attacks: This refers to sudden loss of consciousness, presenting anytime, anywhere and in any position without any reason. Bystanders usually notice that the patient becomes pale, pulseless, and loses consciousness. The duration of the attack is usually short but convulsions may be present if it continues long enough to cause serious cerebral ischaemia. Any condition that decreases cerebral blood flow can cause Stokes-Adams attacks.

- Fatigue.

- Heart failure.

- Dizziness.

On examination the patient has a regular bradycardia, and cannon waves are visible in the neck veins when the atrium contracts against a closed tricuspid valve. The intensity of

the first heart sound may vary as the degree of ventricular filling varies. For the same reason an ejection murmur may be present when the stroke volume is increased.

Treatment

Acute Third-Degree Block

A temporary pacemaker electrode must be positioned without delay. The pacemaker is usually set at 70-90 beats per minute. If facilities for pacing are unavailable a positive chronotropic agent, for example, isoprenaline, may be used. An infusion containing 0.2 mg of isoprenaline in 1000 mL of 5% dextrose water may be titrated at 5-40 drops per minute. This usually increases the heart rate, but the drug is also arrhythmogenic and may cause ectopic ventricular beats and even ventricular tachydysrhythmias. It should therefore be reserved for emergency use only, i.e. when the ventricular rate is very slow and the patient has symptoms of serious cardiovascular dysfunction, and no other treatment is available. Atropine has no place in the treatment of this condition.

Chronic Thid-Degree Heart Block

Patients with symptoms should receive a permanent pacemaker. Some asympatomatic patients may not need a pacemaker. Patients with congenital AV block usually have an acceptable heart rate. In this group the block is usually in the proximal part of the bundle of His with an escape rhythm of approximately 40-60 beats per min. Exercise will also increase the heart rate to a certain extent in these patients. Nevertheless, most patients with a third-degree AV block will require a pacemaker at some stage because of progressive cardiovascular decompensation.

Chapter 3.4: Shock

C. J. Mieny, G. W. Geelhoed

Definition of Shock

Shock is characterized by a state of microcirculatory hypoperfusion which at first leads to reversible ischaemic-induced cellular injury. If the process is sufficiently severe or protracted it ultimately eventuates in irreversible cellular-organ injury and dysfunction. The precise mechanisms responsible for the transition from reversible to irreversible injury and death of cells are not clearly understood although the biochemical-morphological sequence in the progression of ischaemic cellular injury has been fairly well elucidated. There is now hope that by understanding the events leading to cell injury and death we may be able to therapeutically intervene in shock by protecting sublethally injured cells from irreversible injury and death.

The simplest and most appropriate definition encompassing all the phenomena leading to cell injury should be used. Shock is *insufficient nutrient flow*. In this three-term definition each term is important.

Insufficiency: *This relates to a supply inadequate for a demand. In order to have*

insufficiency one could have a deficit in supply or an increase in demand. For example, a cardiac output of 5 L/min may be sufficient for the energy requirements at rest but totally insufficient in a patient after injury with sepsis and fever.

Nutrient: For immediate energy requirements cellular metabolism is directed toward the generation of biologically useful energy in the form of high-energy phosphate bonds. Free energy is generated by oxidative phosphorylation and the production of Adenosine triphosphate (ATP). *Substrates to be oxidized for this purpose include glucose, fatty acids, ketons, glycerol and de-aminated amino acids.*

In shock with a decrease in oxygen tension in the cell there is a loss of oxidative phosphorylation with a decrease of mitochondrial ATP production. There is also impaired activity of cell membrane-associated enzymes such as ATPase, and maintenance of normal membrane function and permeability is altered.

Flow: Since flow can be measured in numbers it becomes an important aspect of the clinical diagnosis of shock and its management.

Measurements in Shock

In physics flow is directly related to pressure and inversely to resistance. This universal flow formula is not dependent on the type of fluid and is also applied to the flow of electrons. In electricity it is expressed as Ohm's law. This law applies just as appropriately to bloodflow.

Flow = Pressure/Peripheral Resistance

From this law it can be deduced that shock is just as well a state of elevated resistance as it is a state of low blood pressure. *However the focus should remain on flow rather than simply on pressure since most drugs that result in a rise in pressure do so by raising the resistance, which in turn decreases flow.*

Cardiac Output

Blood flow is dependent on cardiac output. Three factors determine cardiac output - preload or the volume entering the heart, contractility of the heart, and afterload or the resistance against which the heart must function to deliver the nutrient flow. These three factors are interrelated to produce the systolic ejection from the heart. Up to a point, the greater the preload the greater the cardiac output. As myocardical fibres are stretched by the preload the contractility increases according to the Frank-Starling principle. However, an excessive increase in preload leads to symptoms of pulmonary/systemic venous congestion without further improvement in cardiac performance. The preload is a positive factor in cardiac performance up the slope of the Frank-Starling curve but not beyond the point of cardiac decompensation.

Contractility of the heart is improved by inotropic agents. The product of the stroke volume and the heart rate equals the cardiac output. Cardiac output acting against the peripheral resistance generates the blood pressure. Diminished cardiac output in patients with

pump failure is associated with a fall in blood pressure. To maintain coronary and cranial blood flow there is a reflex increase in systemic vascular resistance to raise blood pressure. An exaggerated rise in systemic vascular resistance can lead to further depression of cardiac function by increasing ventricular afterload. Afterload is defined as the wall tension during left ventricular ejection and is determined by systolic pressure and the radius of the left ventricle. Left ventricular radius is related to end-diastolic volume, and systolic pressure to the impedance to blood flow in the aorta, or total peripheral vascular resistance.

As the emphasis in the definition of shock is on flow, we should be looking for ways to measure flow.

Indirect Measurement of Flow

In many patients in shock, simply laying a hand upon their extremities will help to determine flow by the cold clammy appearance of hypoperfusion. But probably the most important clinical observationb to determine adequate nutrient flow to a visceral organ indirectly will be the urine output.

The kidney responds to decreased nutrient flow with several compensatory changes to protect its own perfusion. Over a range of blood pressure the kidneys maintain a nearly constant blood flow. If the blood pressure decreases, the kidney's autoregulation of resistance results in dilation of the vascular bed. It keeps nutrient flow constant by lowering the resistance even though the pressure has decreased.

If the blood pressure falls further and a true decrease in flow across the renin/angiotensin mechanism is triggered, renin from the juxtaglomerular apparatus acts upon angiotensin from the liver. The peptide is cleaved by renin and a decapeptide results, which in the presence of converting enzyme clips off two additional aminoacids to produce the octapeptide angiotensin II, one of the most potent vasopressors known. The third step is that the same octapeptide stimulates the zona glomerulosa of the adrenal cortex to secrete aldosterone which causes sodium retention and results in volume expansion. *The kidney has thus carried out three methods of protecting its perfusion. Autoregulation, pressor secretion and volume expansion.* When all three compensatory mechanisms have failed, there is a decrease in the quality and quantity of urine as a function of nutrient flow to this organ. Urine flow is such an important measurement of flow in the patient in shock that we can use this to define the presence or absence of shock. For practical purposes, if the patient is producing a normal quantity of normal quality urine, he is not in shock.

Another vital perfusion bed that reflects the adequacy of nutrient flow is the brain itself. Since adequate nutrient flow is a necessary, although not the only requirement for cerebration, *consciousness can also be used to evaluate the adequacy of nutrient flow in the patient with shock.*

Direct Flow Measurement

Venous Pressure

Between the heart and the groins or axillae there are valveless venous reservoirs where the veins reflect filling pressures more directly than extrinsic pressures. Thus a central venous pressure may be used to assess flow volumes entering the heart. *As a general rule if a patient in shock has both systemic arterial hypotension and central venous hypotension the shock is due to volume depletion. On the other hand, if central venous pressure is high though arterial pressure is low, shock is not due to volume depletion and is more likely due to pump failure.*

Pulmonary Arterial Pressure

The lesser circulation is a valveless system through which flows the entire cardiac output from the right side of the heart. The pulmonary circulation can be entered from the periphery through the use of a flow-directed catheter. In its passage from the superior vena cava through the right atrium, from which it migrates into the right ventricle on a myocardial contraction, the balloon tip flips through the pulmonic valve exactly like a pulmonary embolus, until the balloon tipped catheter wedges in a pulmonary artery. Along the way the distal lumen can be used to measure pressures, and components of the blood flow. Pressures can be obtained in each of the chambers including right atrial pressure, right ventricular pressure and pulmonary wedge pressure. *After wedging, the pressure transmitted to the catheter represents pulmonary vein pressure and thus left atrial pressure. The wedged pulmonary arterial pressure is a useful approximation of left ventricular end-diastolic pressure (LVEDP). LVEDP usually correlates with left ventricular end-diastolic volume.*

Cardiac output can be measured with the thermodilution technique. A solution that is cooler than body temperature is injected into the right atrium and the resultant drop in blood temperature at the catheter tip is used to calculate cardiac output. By estimating oxygen saturation in the pulmonary artery, blood oxygen extraction can be determined.

Systemic Arterial Pressure

The radial artery or brachial artery can be catheterized for pressure measurements and determination of arterial blood gases. *Arterial bloodgas determination may be more significant than the pressure measurements since it may give an indication of metabolism in shock.*

Metabolism in Shock

The ultimate measurement of the impact of shock must be at the cellular level. The most convenient measurement is a determination of the blood gases. Measurement of pO_2, pCO_2, pH and arterial lactate will supply information on oxygen delivery and utilization of energy substrates. Both pO_2 and pCO_2 are concentrations - partial pressure of oxygen and carbon dioxide. *If the pCO_2 is normal, there is adequate alveolar ventilation. CO_2 is one of the most freely diffusable gases in the body and is not overproduced or under-diffused.* Consequently its partial pressure in the blood is a measure of its excretion through the lung which ia a direct result of alveolar ventilation. *The pO_2 is a similar concentration but it is the partial pressure of oxygen in the blood and not of the oxygen content.* A concentration

measure in the blood does not tell us the delivery rate of oxygen to tissues per unit of time without knowing something of the blood flow that carried this concentration.

For evaluation of oxygen utilization, however, data is obtainable from arterial blood gases that can indicate what the cells are doing metabolically, which is the most important reflection of the adequacy of their nutrient flow. The pH is the hydrogen ion concentration which can be determined easily and quickly. The lactate and pyruvate concentrations can be measured but this is more time consuming. The pH and the two carbon fragment metabolites are very important indicators of cellular function in shock.

In shock there is a fundamental shift in metabolism. When there is adequate nutrient flow, glucose and oxygen are coupled to produce in glycolysis the high energy phsophate bonds necessary for energy exchange. This process of aerobic metabolism also produces two freely diffusable byproducts - carbon dioxide and water - both of which leave the body by excretion through the lung and the kidney. Aerobic metabolism is efficient, therefore there is no accumulation of any products of this catabolism, a high yield of ATP is obtained from this complete combustion of metabolites.

When there is inadequate delivery of nutrients and oxygen, as occurs in shock, the cells shift to anaerobic metabolism. There are immediate consequences of anaerobic metabolism in addition to its inefficient yield of energy. In the absence of aerobic metabolism, energy extraction takes place at the expense of accumulating hydrogen ion, lactate and pyruvate, which have toxic effects on normal physiology. These products of anaerobic metabolism can be seen as the "oxygen debt". There is some buffer capacity in the body that allows this debt to accumulate within limits but it must be ultimately be paid off.

Acidosis has significant consequences in compensatory physiology. In the first instance, oxyhaemoglobin dissociates more readily as hydrogen ions increase. However, there is a significant toxicity of hydrogen ions as well. Despite the salutory effect on oxyhaemoglobin dissociation, the hydrogen ion has a negative effect on oxygen delivery. Catecholamines speed up the heart's rate and increase its contractile force and the product of this inotropic and chronotropic effect is an increase in cardiac output. *Catecholamines, however, are physiologically effective at alkaline or neutral pH. Therefore, and acid pH inactivates this catecholamine method of compensation for decreased nutrient flow.* For example, if a catecholamine like isoproterenol is administered to a patient in shock, it would increase myocardial contractility and heart rate and also dilate the periphery to increase nutrient flow to these ischaemic circulation areas. However, the ischaemic areas have shifted to anaerobic metabolism accumulating hydrogen ion, lactate and pyruvate. When the circulation dilates, this sequestrated oxygen debt is dumped into the central circulation and the drop in pH inactivates the catecholamines circulatory improvement as effectively as if the infusion of the agent has been interrupted.

Classification of Shock

The classification of shock is of practical importance if the pathophysiology is understood in terms that make a fundamental difference in treatment. Although the basic definition of shock *"insufficient nutrient flow"*, remains inviolate, four types of shock, based on a distinction not only in the pathophysiology but also in the management of the patients,

are recognized.

Hypovolaemic Shock

Hypovolaemic shock is caused by a decrease in the intravascular volume of over 20% of predicted normal. It is characterized by significant decreases in filling pressures with a consequent decrease in stroke volume. Cardiac output is temporarily maintained by a compensatory tachycardia and reflex increases in peripheral vascular resistance and myocardial contractility mediated by neurohumoral mechanisms. *When the blood volume loss exceeds 30% the compensatory mechanisms are no longer effective and the decrease in cardiac output causes a decreased oxygen transport to peripheral tissues. These tissues attempt to maintain their oxygen consumption by increasing oxygen extraction. Eventually this compensatory mechanisms also fails and tissue hypoxia leads to lactic acidosis, hyperglycaemia and failure of the sodium pump with swelling of the cells from water influx.*

Clinical Presentation

The classic features of hypovolaemic shock are hypotension, tachycardia, pallor, sweating, cyanosis, hyperventilation, confusion and oliguria. Cardiac function can be depressed without gross clinical haemodynamic manifestations. The heart shares in the total body ischaemic insult. Systemic arterial hypotension increases coronary ischaemia causing rhythm disturbances and decreased myocardial performance. As the heart fails, left ventricular end-diastolic pressure rises, ultimately causing pulmonary oedema.

Hyperventilation may maintain arterial pO_2 at near normal levels but the pCO_2 falls to 20-30 mm Hg (2.7-4 kPa). Later pulmonary insufficiency may supervene from alveolar collapse and pulmonary oedema resulting from damaged pulmonary capillaries, cardiac failure or inappropriate fluid therapy.

Renal function is also critically dependent on perfusion. Oliguria is an inevitable feature of hypovolaemia. During volume loss renal blood flow falls correspondingly with the blood pressure. *Anuria sets in when the systolic blood pressure falls to 50 mm Hg. Urine output is a good indicator of peripheral perfusion.*

Cardiogenic Shock

Cardiac function is impaired in shocked patients even if myocardial damage is not the primary cause. Reduced myocardial function in shock includes arrhythmias, myocardial ischaemia from systemic hypertension and alterations in blood flow, and myocardial lesions from high circulatory levels of catecholamines, angiotensin and possibly a myocardial depressant factor. The cardiac etiologies of hypotension and shock all invariably produce reduced cardiac output as the primary haemodynamic abnormality. This can be caused by:

- *Impaired myocardial contractility as in ischaemia, infarction and cardiomyopathy.*

- *Conduction system disturbances (bradidysrhythmias and tachydysrhythmias) and mechanical complications of acute myocardial infarction - acute mitral valvular regurgitation and ventricular septal rupture.*

- Impaired diastolic filling because of restriction of the motions and filling of the heart by pericardial tamponade.

Other forms of cardiogenic shock include those clinical examples in which the patient may have a nearly normal resting cardiac output but cannot raise the cardiac output under circumstances of stress because of poor myocardial reserves due to pharmacologic beta adrenergic blockade, for example propranolol for hypertension. Heart failure and dysrhythmias are discussed in depth elsewhere in this book.

Clinical Presentation

The clinical picture will depend on the underlying cause. Clinical signs of peripheral vasoconstriction are prominent, pulmonary congestion is frequent and oliguria is almost always present. Pulmonary oedema may cause severe dyspnoea central cyanosis and crepitations, audible over the lung fields and lung oedema visible on x-rays.

Signs on cardiac examination depend on the underlying cause. A systolic murmur appearing after myocardial infarction suggests mitral regurgitation or septal perforation.

Haemodynamic findings consist of a systolic arterial pressure less than 90 mm Hg decreased cardiac output, usually less than 1.8 $L/m^2/min$, and a pulmonary arterial wedge pressure (PAWP) of greater than 20 mm Hg (2.7 kPa). Sometimes cardiogenic shock occurs without the PAWP being elevated. This may be a result of diuretic therapy or plasma volume depletion by fluid lost into the lungs. Patients with relative hypovolaemia below the levels where there is a risk of pulmonary oedema and finally patients with significant right ventricular infarction and right heart failure will also not have elevated PAWP. These patients although their shock is cardiogenic, will respond dramatically to plasma volume expansion and deteriorate if diuretics are given.

Peripheral Pooling

A third type of shock results from sequestration of blood from the general circulation so that it becomes unavailable as nutrient flow. *A very simple example of this type of shock is syncope. It is caused by a strong vagal discharge resulting in dilatation of the small vessels of the splanchnic bed.* The next cycle of the heart would have less venous return so that the ventricle would not fill and the next stroke volume would not adequately perfuse the cerebrum causing a faint. No blood was lost but there was a sudden increase in the amount of blood trapped in one part of the circulation and where it was no longer available for perfusion to one obligate, aerobic glycolytic metabolic bed - the central nervous system.

This same dilatation of the capacitance reservoirs in the body occurs with endotoxic shock. Endotoxin can have a major effect on this form of peripheral pooling and even though the blood volume is normal the distribution of that volume is changed so that there is insufficient nutrient flow where aerobic metabolism is needed.

Endotoxin also has other consequences which may cause the fourth type of shock.

Cellular Defect Shock

In the ultimate analysis all shock leads to cellular defect shock. Aerobic metabolism takes place in the cytochrome system in the cristae of the mitochondria. Oxidative phosphorylation in the cytochrome system produces high-energy phosphate bonds by coupling oxygen and glucose, forming the freely diffusable by-products carbon dioxide and water. *Several poisons uncouple oxidative phosphorylation but the most common in clinical practice is endotoxin.* Sepsis is very frequent in hospitalized patients and endotoxic shock is distressingly common. *There is fever, tachycardia may or may not be present, the mean blood pressure is usually below 60 mm Hg, yet the cardiac output varies between 3 and 6 L/m^2/min.* This haemodynamic state is indicative of low peripheral vascular resistance.

In addition to low peripheral resistance as a cause of hypotension in septic shock there are three other causes of the inability of the cardiovascular system to maintain the cardiac output at a level sufficient to maintain normal blood pressure:

- *Hypovolaemia due to fluid translocation from the blood into interstitial spaces.*

- *Elevated pulmonary vascular resistance due to ARDS.*

- *Bioventricular myocardial depression manifested by reduced contractility and an inability to increase strokework.*

The ultimate cause of death in septic shock is failure of energy production at cellular level as reflected by a decline in oxygen consumption. It is not only the circulatory insufficiency which is responsible for this but also the impairment of cellular oxidative phosphorylation by endotoxin or endogenously produced superoxides. There is a narrowing of arterial-mixed venous oxygena difference as an indication of reduced oxygen extraction, which often precedes the fall of cardiac output. Anaerobic glycogenolysis and a severe metabolic acidosis due to lactacidaemia result. The mechanisms responsible for the phenomena observed in sepsis and endotoxic shock are discussed in great detail elsewhere in this book.

Post-Shock Sequence and Multiple Organ-Failure Syndromes

Although the consequences of sepsis following trauma and shock, the metabolic response to trauma, and multiple organ failure are discussed in detail elsewhere in this book, it is important to briefly reiterate the usual sequence of events following shock to enable a logical discussion of the management of shock.

The ultimate cause of death in shock is failure of energy production as relfected by a decline in oxygen consumption (VO_2) to values less than 100 mL/m^2/min. *Circulatory insufficiency is responsible for this energy crisis compounded by impairment of cellular oxidative phosphorylation by endotoxin and such endogenously produced substances as superoxides.*

In shock, whether hypovolaemic or septic, energy production is insufficient to satisfy the requirements. In the presence of oxygen deprivation and cellular injury, the conversion

of pyruvate to acetyl-CoA for entry into the Krebs cycle is inhibited. *Lactic acid accumulates and the oxidation-reduction potential falls although lactate is normally used by the liver via the Cori cycle to synthesize glucose.* Hepatic gluconeogenesis may fail in hypovolaemic and septic shock because of hepatocyte injury and inadequate circulation. The lactacidaemia cannot be corrected by improvement of circulation and oxygen delivery once the cells are irreparably damaged.

In the low-output shock-state plasma concentrations of free fatty acids and triglycerides rise to high levels because ketone production by beta-oxidation of fatty acids in the liver is reduced suppressing the acetoacetate to betahydroxybutarate ration in the plasma.

The post-shock sequelae of inadequate nutrient flow therefore is progressive loss of cell function. The rate at which this loss occurs depends upon the cell's ability to switch its metabolism, to convert alternate fuels to energy, the increased extraction of oxygen from oxyhaemoglobin and the compensatory collaboration of failing cells and organs whereby nutrients may be shunted selectively to more critical systems. Not all cells are equally sensitive to shock nor similarly refractory to restoration of function when adequate nutrient flow is restored.

As cells lose function the reserves of the organ composed of those cells are depleted until impaired function of the organ results. These organs function in systems and a "system failure" results. Multiple systems failure occurring in sequence leads to the collapse of the organism.

Management of the Shocked Patient

The purpose for distinguishing the different pathophysiologic mechanisms of shock becomes important when treatment has to be initiated. *The final all-encompassing aim of treatment is to restore aerobic cellular metabolism timeously.* This requires restoration of adequate flow of oxygenated blood, which is dependent on optimal oxygenation, adequate cardiac output and restoration of aerobic cellular metabolism. *These aims can be achieved by securing a patent airway and controlled ventilation if alveolar ventilation is inadequate. Restoration of optimal circulating blood volume, enhancing cardiac output through the use of inotropic agents or increasing systemic vascular resistance through the use of vasopressors, the correction of acid-base disturbances and metabolic deficits and the combating of sepsis are all vital in the management.*

Ventilation

The traumatized, hypovolaemic or septic patient has an oxygen demand that often exceeds twice the norm. Under these circumstances hyperventilation would provide an effective means of increasing oxygen delivery. The traumatized shocked patient usually cannot exert this additional effort and therefore often develops respiratory failure followed by respiratory acidosis.

In some patients an oxygen mask may be enough to maintain efficient oxygen delivery. In more severe cases, endotracheal intubation and ventilatory assistance may be necessary. Ventilatory assistance is discussed in detail elsewhere in this book. Severely

shocked patients must be intubated early to avoid respiratory failure. *As a general rule the following criteria can be used as indications for intubation and ventilatory support.*

- Important clinical signs that ventilatory support is necessary include cyanosis, severe tachypnoea or bradypnoea and mental obtundation.

- A respiration rate of 30 or more per minute and excessive ventilatory effort.

- A pCO_2 of greater than 45 mm Hg with metabolic acidosis, or greater than 50 mm Hg with normal bicarbonate levels.

- pO_2 less than 60 mm Hg on 40% O_2.

- Tidal volume less than 5 mL/kg.

- Vital capacity less than 10 mL/kg.

- Minute ventilation less than 8 L/min.

If ventilatory support is instituted the goals are relatively specific.

The respiratory rate should be adjusted to ensure a pCO_2 of between 35 and 40 mm Hg. This will avoid respiratory alkalosis and will also avoid a shift of the oxyhaemoglobin dissociation curve to the left, which results in an increased affinity for oxygen and significantly decreases oxygen availability to tissues which will require increased cardiac output to maintain tissue oxygenation. The arterial pO_2 should be maintained between 80-100 mm Hg with the lowest possible oxygen concentration.

If this cannot readily be achieved, oxygen concentration may have to be increased or end-expiratory pressure increased to increase the functional residual capacity of the lungs. Pressures less than 20-22 cm water are desirable to avoid barotrauma. Tidal volumes of between 10 and 13 mL per kg body weight are usually needed to respond to the increased metabolic and oxygenation requirements of shocked patients.

It has been shown that respiratory muscles require a disproportionate share of the total cardiac output and therefore other organs are deprived of necessary blood flow and lactic acidosis is potentiated. *Mechanical ventilation tends to reverse this lactic acidosis.*

Fluid Therapy for Volume Expansion

Although considerable controversy exists regarding the type of fluid to be administered for volume expansion in hypovolaemic shock, it is reasonable to use a fluid that includes the kind of fluid being lost. Blood in the case of haemorrhage, and crystalloid solutions in the case of diarrhoea or burns. Despite many studies, no convincing evidence exists that favours any specific fluid regimen. Balanced salt solutions (BSS) are effective volume expanders for the initial resuscitation of patients with shock. For most patients Ringer's lactate solution is the preferred crystalloid solution. The lactate acts as a buffer and is eventually metabolized to carbon dioxide and water. However, septic patients with significant hepatic dysfunction do

not metabolize lactate well and for these patients other balanced salt solutions are preferred.

In hypovolaemic shock a volume of solution in excess of measured losses is generally required to effectively resuscitate the patient. Initially 2 to 3 litres of crystalloid is given and the response of pulse rate, blood pressure and urinary output monitored. If this fails to correct haemodynamic abnormalities, *additional crystalloid solution and blood is indicated, because crystalloids in large quantities will ultimately cause a dilutional effect which can decrease the blood's oxygen-carrying capacity.* It is true that the restored vascular volume will increase the cardiac output and thus maintain tissue oxygenation. *This increased cardiac output can be sustained by the normal heart but in the diseased heart or the elderly patient, it is safer to give blood earlier to obviate the possibility of cardiac failure.*

In many countries packed red blood cells with crystalloid solutions instead of whole blood is given because the blood banking industry in those countries has changed to component therapy to the extent that whole blood replacement is not readily available for large-volume transfusion.

The colloid versus crystalloid controversy has now been laid to rest after prospective clinical trials which showed that albumin supplementation was associated with a transient expansion of plasma volume and an increased renal blood flow, but a fall in glomerular filtration rate (GFR). Decreased filtration resulted and this caused a reduction in excretion of sodium, osmoles and water. Reduced renal excretion caused an increased weight gain which was associated with elevated central filling pressures. Pulmonary oxygenation worsened and physiological shunting in the lung deteriorated. The patients who received albumin required prolonged ventilatory support and had a higher mortality rate.

A practical approach to the patient in hypovolaemic shock is the following. Give 3 litres of balanced salt solution for each litre of blood loss when this can be estimated. Because this is often difficult, the most sensible method is to institute a fluid challenge. Give BSS at a rate of 1000 to 2000 mL/h. Vital signs and the pulmonary artery wedged pressure (PAWP) are checked every 10 minutes. If the pressure is below 10 mm Hg the rate of fluid resuscitation should be increased. If the pressure rises to 25 mm Hg fluid resuscitation should be restricted.

It is also recommended that PAWP should be correlated with cardiac output or stroke volume. A low cardiac output associated with a low PAWP requires volume infusion to increase the filling pressure of the left ventricle thus increasing the stroke volume. When the optimum PAWP of ± 18 mm Hg is exceeded, stroke volume may be enhanced by using inotropic drugs.

Pharmacologic Support of Blood Pressure

Stroke volume is controlled by ventricular preload, afterload and contractility. Preload is mainly influenced by the volume of circulating blood but afterload and contractility can be manipulated by pharmacological agents.

Reducing the systemic vascular resistance with vasodilators can be a very effective means of improving cardiac output when systemic pressure or cardiac filling pressures are

normal or elevated.

Nitroprusside is especially useful in these circumstances and has balanced vasodilating effects on both the arterial and venous circulations, thus minimizing adverse effects on arterial blood pressure. Prostaglandin E_2 may also be an effective reducer of cardiac afterload. Reducing afterload can be very dangerous during shock if systemic pressures or cardiac filling pressures are low.

A number of drugs have been shown to improve cardiac contractility by their inotropic effects. Dopamine and dobutamine are the most commonly used inotropic drugs in the treatment of shock. *Dopamine is an endogenous precursor of noradrenaline and has multiple dose-related effects. At low doses (> 5 nanog/kg/min) beta-2 and dopaminergic effects increases blood flow to renal and splanchnic beds increasing renal perfusion and urine output. At higher doses (> 10 nanog/kg/min) cardiac inotropy predominates but at even higher doses, vasoconstriction predominates.*

Dobutamine is a synthetic substance which increases cardiac output with little change in peripheral resistance and with only moderate increases in heart rate.

Isoproterenol and adrenaline are also effective inotropic agents. The disadvantage of isoproterenol is that it increases the heart rate, and that of adrenaline that it increases peripheral resistance as well as ventricular irritability and is therefore probably contraindicated in hypovolaemic shock.

Digoxin enhances cardiac contractility but its use in shock is limited because it takes considerable time to act. In the intensive care situation digoxin is usually reserved for the treatment of supraventricular tachycardias.

The Post-Shock Sequestration Phase

After cessation of bleeding and restoration of the intravascular fluid compartments, the patient enters into a period of obligatory extravascular fluid sequestration usually lasting 24 to 36 hours. To maintain effective perfusion as judged by blood pressure, pulse, central filling pressure and urine flow, as much as 1 litre balanced salt solution per hour may become necessary. After 36 to 48 hours the mobilization and diuretic phase begins. Plasma volume is now increased due to an autoinfusion of fluid from the interstitial and intracellular fluid compartments as reflected by a rise in mean arterial pressure and pulse pressure, despite a reduction in the rate of fluid infusion.

Therapy in this phase should be aimed at reducing the rate of intravenous infusion and changing from a balanced salt solution to a hypotonic fluid such as 5% dextrose in 1/3 normal saline.

The importance of the management of concomitant sepsis in shock is discussed in detail elsewhere in this book.

Metabolic Manipulations

The endogenous opiate beta-endorphin appears to be involved in the hypotension and impaired tissue perfusion that occur in both hypovolaemic and septic shock states, as elevations in this substance can be demonstrated at the time that these physiologic changes take place.

Naloxone, an opiate antagonist, has been shown to elevate blood pressure and cardiac output and to significantly improve survival in septic and haemorrhagic shock models. Early results in shock patients have supported these findings. Prostaglandins have also been implicated in shock. They may play a role in the pathophysiology of shock by vasodilation or vasoconstriction of the microcirculation with shunting of blood. Experimental evidence exists that cyclo-oxygenase inhibitors like indomethacin and ibuprofen can improve the haemodynamic state in experimental shock.

Prognosis in Shock

The prognosis of the shocked patient depends on the duration of the shock, the underlying cause, the pre-existing vital organ function. The prognosis is best when the duration is kept short by early recognition and aggressive correction of the circulatory disturbance and when the underlying cause is known and corrected.

Occasionally shock does not respond to standard therapeutic measures. Unresponsive shock requires an understanding of the potential occult causes of persistent physiologic disturbances.

These correctable causes include:

- Underappreciated volume need with inadequate fluid resuscitation and a failure to assess the response to a fluid challenge.

- Erroneous presumption of overload when cardiac disease is also present.

- Hypoxia caused by inadequate ventilation, barotrauma to the lung, pneumothorax or cardiac tamponade.

- Undiagnosed or inadequately treated sepsis.

- Uncorrected acid-base or electrolyte abnormalities.

- Endocrine failure like adrenal insufficiency or hypothyroidism.

- Drug toxicity.

Comment

Colloids and Crystalloids in Resuscitation

J. P. Pretorius

Restoring intravascular volume in patients suffering from burns, sepsis, trauma, major surgery, diabetic ketoacidosis, heat stroke and even a large percentage of patients with acute myocardial infarction, is essential to enhance cardiac performance and to provide adequate tissue perfusion and oxygenation. For successful fluid resuscitation of shock states, it is necessary to understand the pathophysiologic mechanisms of fluid shift and haemodynamic changes occurring during shock. Blood, blood components, synthetic colloids and crystalloid solutions are available for transfusion. Questions arising during fluid therapy are: when to start, how much to give, which solution to use and how to monitor the intravascular volume accurately. Although clinicians are unanimous about the importance of fluid therapy in the treatment of critically ill patients, the choice of the most suitable fluid for rapid resuscitation remains controversial.

Replacing blood loss is clearly necessary and best achieved by the use of crossmatched whole blood if time allows, otherwise type specific O-negative blood. There is also little argument about the need to replace fasting volume deficits and maintenance fluids perioperatively. Choosing the ideal extracellular volume expander is more difficult because extensive support may be found for both colloid and crystalloid solutions. *The colloid/crystalloid controversy revolves around the effect of each on pulmonary function.* The proponents of crystalloid fluid therapy maintain that reduced extracellular water is an important defect in shock states, which can be corrected best by administering large volumes of crystalloids which will also restore intravascular volume quickly and safely. Because less than 25% of infused crystalloids are retained in the intravascular compartment after one hour, *two or four times more times more crystalloid than colloid is necessary to achieve haemodynamic stability at the same physiologic end points. This may cause gross peripheral oedema and an increase in body weight, but does not cause pulmonary oedema, provided the PAWP is kept ≤ 15 mm Hg.*

Proponents of colloid therapy regard hypovolaemia as the primary defect in shock. They believe that colloid fluids promptly restore plasma volume and re-establish haemodynamic stability with substantially smaller volumes of fluid because after one hour, almost all the iso-oncotic colloid is still present in the intravascular space.

The total body water exists within discrete fluid compartments - the intracellular compartment, and the extracellular compartment, which can be subdivided into the interstitial compartment and the intravascular compartment. The interstitial fluid bathes the cells and allows metabolic substrates and waste products to diffuse between the capillaries and the cells. Excess free interstitial fluid is returned to the intravascular compartment via lymphatic channels. Interstitial fluid mostly exists within a proteoglycan matrix in gel form, which allows easy diffusion of solutes through the interstitium but retards bulk water flow and maintains the shape of tissues.

The fluid compartments are separated by semi-permeable membranes which are freely

permeable to water but retard diffusion of cations and other solutes. Osmosis determines the fluid distribution between the compartments depending on differences between intracellular and extracellular osmotic concentrations.

The intravascular space or circulating blood volume is the smallest compartment but the only one amenable to volume estimation by invasive and non-invasive measurements and biochemical analysis. The interstitial and intracellular compartments are considered together for purposes of fluid assessment because it is almost impossible to differentiate between them on clinical grounds. They contain most of the body fluid but are inaccessible to volume and biochemical analysis.

According to Hillman, it is important to understand fluid compartments and their clinical assessment because the solutions available for transfusion are distributed in a predictable fashion. *Blood and colloids are confined mainly to the intravascular space, because they contain large colloid osmotic particles. Crystalloid solution such as Ringer lactate and isotonic saline which have no inherent oncotic pressure are distributed mainly to the interstitial space. Solutions such as 5% glucose are distributed proportionately between the three spaces.* As the intracellular space is the largest, most of the fluid will be distributed intracellularly.

The effect of albumin and other plasma proteins can be expressed by measurement of the plasma colloid oncotic pressure (COP) which is the focus of the debate. Colloid solutions maintain COP but crystalloid solutions cause haemodilution and can lower the COP. The forces operating at all capillary membranes determining fluid flux between the intravascular and interstitial spaces, were expressed by Starling in the following equation:

Q = K (Pmv - Ppmv) - sigma(pimv - pipmv).

This equation can be simplified to:

Q = K (PAWP - 0.24 COP).

Q - net fluid flux across the capillary membrane.

K - permeability of the capillary membrane to fluids.

This equation demonstrates that decreases in COP after crystalloid administration are only 25% as important as increases in hydrostatic pressure in increasing fluid exchange. This explains why pulmonary oedema does not develop during crystalloid resuscitation, provided the hydrostatic pressures are not elevated. It also indicates that there exists a fundamental difference between the pulmonary microvascular forces and those in systemic capillary beds. *Systemic capillaries are "tighter" to protein filtration than pulmonary capillaries* - in systemic tissue the interstitial protein level may be 20-30% of intravascular values, resulting in a large transcapillary oncotic gradient. This explains why peripheral tissues are more sensitive to haemodilution than the lung, and why patients develop marked peripheral oedema after crystalloid resuscitation. *In the lung where the capillaries are normally more permeable to proteins than in the systemic circulation, the interstitial oncotic pressure may be as high as 70% of the intravascular value.* Another efficient oedema-preventing mechanism in the lung

is the fact that after crystalloid haemodilution the plasma oncotic pressure is reduced and this is followed by a decrease in pulmonary interstitial COP and a lung-lymph flow which increases manyfold.

Several studies have examined the COP-PAWP gradient as a simplification of the Starling equation in an attempt to predict the development of pulmonary oedema. Tranbaugh has shown in burn and trauma patients, "that sepsis is the primary determinant of pulmonary oedema". The decreased COP levels are associated with sepsis but unrelated to pulmonary oedema formation, as long as the PAWP is below 15 mm Hg. Nevertheless, from the work of Rackow *et al* it does appear that a threshold of ± 5 mm Hg exists for the COP-PAWP gradient below which pulmonary oedema develops. They suggest that assessment of the COP-PAWP gradient during resuscitation with either colloid or crystalloid solutions remains a valuable guide for fluid therapy.

Many experimental studies using a variety of animal models as well as clinical studies in varied groups of somewhat sick and very sick patients have been undertaken to examine the use of colloids and crystalloids. Although some differences in physiologic variables have been noted between the groups, the incidence of ventilatory failure or adult respiratory distress syndrome has not varied greatly among the groups provided fluid overload of either type was prevented. At present the search continues to delineate groups of patients for whom colloid therapy might be particularly useful. This might be the case in serious sepsis, the elderly, cardiovascular disease, respiratory disease, protracted shock and multiple organ failure.

Considering all the facts, the proponents of crystalloid therapy suggest that given the much greater cost of colloid solutions, the absence of any consistent evidence of benefit and the lack of increased risk of pulmonary oedema without their use, the further employment of colloids in clinical medicine cannot be justified. They also reason that the pronounced peripheral oedema does not have any harmful consequences. There are indications, however, that the extravascular hydrostatic pressure may increase to such an extent that the microvessels may become compressed and consequently the available capillary surface area for exchange processes therefore remains low, explaining the poor tissue oxygenation and clearance of metabolites following crystalloid-treated hypovolaemic shock. On the other hand, colloids when used for shock therapy, will not only efficiently increase blood volume, cardiac output and central haemodynamics but also enhance nutritive capillary blood flow. *Tissue oedema after crystalloid fluid resuscitation of shock may persist for long periods.*

This may affect wound healing adversely due to tissue hypoxia. Breakdown of oedematous skin, as well as decubitus ulcers may also develop. Cerebral oedema may also be a result of large crystalloid volume loads. As far as cost is concerned, the issue is not the cost of the fluids, but whether the hospital cost is actually decreased by the use of crystalloids. If the total length of hospitalization is prolonged just one day because of persistent oedema, cost savings are no longer present.

Experimental evidence indicates that hypertonic saline decreases intracellular fluid volume and that hyperoncotic colloid decreases both interstitial and intracellular fluid volumes. This leads to expansion of the intravascular volume, haemodilution, and perhaps more importantly, decreased swelling of the injured endothelial cells, thus opening up the critical microcirculation. According to Intaglietta, "the microcirculation in ischaemia, shock

and reperfusion presents mechanical defects in the capillaries that can in part be assigned to low perfusion and transmural pressure. The introduction of hyperosmolar solutions in the circulation corrects this dysfunction through the restoration of arteriolar pressure, the improvement of the capillary flow distribution, endothelial swelling and haemodilution". Is this the final answer?

The body's mechanisms for fluid homeostasis (thirst and urine composition) are normally able to compensate for the most inappropriate fluid therapy. In critically ill patients these mechanisms are usually compromised and therapy must therefore be much more precise. Haljamae suggests that based on the pathophysiological mechanisms of the shock state, *the objective of fluid therapy should be to:*

- *Replenish the intravascular, interstitial and intracellular fluid volumes*

- *Enhance microvascular blood flow*

- *Correct acid-base disturbances*

- *Prevent cell injury during reperfusion*

- *Inhibit activation of the cascade systems*

- *Restore the oxygen-carrying capacity of the blood.*

These objectives can be met using a balanced fluid and volume approach which allows for administration of both crystalloid and colloid.

Chapter 3.5: Cardiac Arrest

C. van der Merwe

Evaluation of a Patient With Suspected Cardiac Arrest

Recognition of Cardiac Arrest (Fig. 3.5.1)

Cardiac arrest may manifest as ventricular filbrillation or asystole, and is recognized by:

- *loss of consciousness*

- *non-palpable central pulses*

- *electrocardiographic (ECG) confirmation.*

Central pulses must always be palpated, when evaluating a patient with suspected cardiac arrest as it may be difficult to detect a peripheral pulse in a collapsed patient. The carotid pulse should be assessed by feeling specifically in the groove formed by the sternocleidomastoid muscle and the thyroid cartilage. The femoral pulses may also be

palpated. Active resuscitation should commence immediately once cardiac arrest has been diagnosed. The ABC of cardiopulmonary resuscitation (Airway, Breathing, Circulation) must be evaluated and restored in rapid succession to optimize the chances of survival.

Establishing the Mechanism of Cardiac Arrest by Means of a Cardiac Monitor

It is necessary to distinguish between ventricular fibrillation and asystole, as further action will differ radically according to the diagnosis.

Establishing and Treating the Cause of the Cardiac Arrest

Evaluation must not interfere with or delay the active resuscitation attempt. The most common causes are classified as precardiac, cardiac and peripheral causes (fig. 3.5.2). Initial action will also be influenced by the status of the blood volume, namely whether the patient is normovolaemic (i.e. acute myocardial infarction), hypovolaemic (i.e. blood loss) or relatively hypovolaemic (i.e. anaphylactic shock).

Figure 3.5.2. Most Frequent Causes of Cardiac Arrest

Precardiac Causes (Volume + Respiratory Disturbances)

- hypovolaemia
- hypoxia
    - upper respiratory tract
    - inhalation of gastric contents
    - drug(s) overdose
    - deep anaesthesia
    - near drowning
    - severe lung disease
- inhalation of poisonous gasses
- hypercapnoea
- electrolyte disturbances (especially potassium)
- acid-base disturbances
- tension pneumothorax
- pulmonary thrombo-embolism
- fat embolism
- hypothermia

Cardiac Causes (Direct Effect)

- ischaemic heart disease
- structural heart abnormalities
- electromechanical dissociation
- pericardial tamponade
- electrical shock
- vagal inhibition
- excess catecholamines
- septicaemia

- hypothermia

Peripheral Causes (Generalized Vasodilation)

- severe blood loss (3rd phase shock)
- anaphylaxis
- drug overdosage
- severe hypothermia
- septicaemia
- deep general anaesthetic

Note that there is an overlap between the different groups in the aetiological classification (i.e. drug overdose). Another important point that the different aetiological groups may be further subdivided into:

- normovolaemic, i.e. ischaemic heart disease

- hypovolaemia, i.e. blood loss

- relative hypovolaemia, i.e. conditions causing vasodilation. The priority of intravenous fluid administration is determined by this further classification.

The in-hospital manegement of a patient with cardiac arrest requires the immediate institution of organized cardiac life support (ACLS) as soon as cardiac arrest has been established.

Advanced cardiac life support (ACLS) comprises standard basic life support measures (BLS) and the use of adjunctive equipment and special techniques for establishing and maintaining adequate ventilation and circulation.

Cardiopulmonary Resuscitation (CPR)

Cardiopulmonary resuscitation may include various actions in the hospital-setting:

- Continuation of ventilation and cardiac compressions and other basic life support measures until advanced cardiac life support (ACLS) techniques can be employed.

- Ventilatory and circulatory support - techniques for establishing and maintaining effective ventilation and circulation.

- Electrocardiographic (ECG) monitoring and the recognition of arrhythmias.

- Electrical therapy.

- Establishment of adequate intravenous (IV) access.

- Drug therapy.

- Treatment of the underlying cause of the cardiac arrest, i.e. suspected or overt acute myocardial infarction, hypovolaemia or anaphylaxis.

- *Recognition and correction of underlying factors such as acidosis, hypoxaemia and hypokalaemia that may be responsible for refractory cardiac arrest.*

Normovolaemic Cardiac Arrest

Immediate Actions

CPR must be instituted immediately. It is essential to obtain help. Resuscitation requires at least two, preferably three trained people.

- Administer sternal thump and begin CPR.

- Ventilation: oxygen via mask and bag provides good ventilation. This eliminates the time wasted in intubation during the critical stage.

- Connect the patient to a monitor. This allows the mechanism of cardiac arrest to be recognized. *The placing of an infusion and intubation are second line priorities!*

    - ventricular fibrillation will show fine or coarse bizarre complexes

    - asysatole will show a straight line.

In any form of cardiac arrest defibrillation must always be initiated first. The reason for this step is that fine ventricular fibrillation can sometimes present as a straight line which resembles asystole.

Ventricular Fibrillation (figure 3.5.3)

With ventricular fibrillation (bizarre complexes on monitor) the following steps are indicated:

- Defibrillation - first with 100-200 J. The electrodes must be correctly positioned. Too high voltage causes unnecessary structural trauma; therefore a higher voltage is only given if necessary.

- Continued cardiac massage and ventilation is essential.

- Administer lignocaine 100 mg IV as a bolus.

- If the sinus rhythm is not restored repeat the defibrillation with a second shock of 200 J. If a third shock is required use 300-400 J. CPR must be continued between the administration of the shocks.

- A lignocaine infusion at 4 mg/minute must be initiated. Solution preparation: 600 mg lignocaine in 200 mL dextrose 5% or 0.9% saline solution. Administration at 80

microdrops per minute delivers 4 mg per minute (or 1.3 mL per minute). With an ordinary infusion set, where 15 drops equal 1 mL, the administration is adjusted to a rate of 20 drops per minute. If hyperexcitability of the myocardium is still present (ventricular tachycardia or extrasystole), the lignocaine dosage is supplemented by intermittent bolus administration of 50 mg IV until the arrhythmia is under control or until a maximum of 200 mg (3 mg/kg) has been administered.

- If sinus rhythm is achieved, but hypotension is still present, dobutamine (dobutrex) is indicated (2.5-10 microgram/kg/min). Preparation: 500 mg dobutamine in 200 mL 0.9% saline solution (not an alkaline solution). Titrate at a rate of 5 to 15 microdrops per minute.

- Once sinus rhythm has been achieved, it is necessary to establish the blood gas and electrolyte status in order to determine the amount of sodium bicarbonate and potassium required. The sodium bicarbonate dose is determined using the following formula: Base excess x mass in kg x 0.3 = mmol $NaHCO_3$.

Half of this dose is administered and a blood gas analysis repeated to assess further needs. Bicarbonate has both alkalinising and osmotic effects. The latter transfers fluid from the interstitial compartment to the vascular compertment. The overloading of the circulation through increased osmotic activity is dangerous in the normovolaemic patient and the maximum dosage for an adult must no exceed 200 mmol.

- If serum potassium is low or with refractory fibrillation, 5-10 mL of a potassium chloride solution (10-20 mmol) is administered through a central catheter in an infusion solution. 2 mL of 50% magnesium sulphate solution given IV reduces ventricular excitability. *Resistant ventricular fibrillation can be the result of acidosis, hypokalaemia or hypoxaemia.*

These conditions must therefore be restored immediately. In resistant VF, 100 mmol sodium bicarbonate and 5 mL of a 15% potassium chloride solution is administered IV empirically while CPR is continued.

Resistant fine fibrillation must be 'coarsened' by the administration of 0.5 mg adrenaline because defibrillation is more effective with coarse ventricular fibrillation. In refractory ventricular fibrillation which still does not react, the use of bretylium tosylate must be considered. The dose is 5 mg/kg and it can be followed by a dose of 10 mg/kg after 15-20 minutes, if required. *Bretylium tosylate increases the fibrillation threshold.*

Asystole (fig. 3.5.4)

With asystole (monitor = straight line) the following steps are taken: Heart massage, ventilation and defibrillation with 400 J must be instituted. Defibrillation is mandatory as ventricular fibrillation is sometimes so fine that it presents as a straight line on the monitor. In these cases defibrillation can be successful. Immediate CPR and defibrillation are always the first priorities.

The following measures are then initiated:

- Atropine 1 mg IV is administered to eliminate vagal effects. The anticholinergic

effect is dependent on the dose. Atropine is administered rapidly.

- Adrenaline 0.5-1 mg IV is administered if no ventricular complexes reappear. The preparation is a myocardial stimulant. In the absence of an intravenous line, 1 mg of adrenaline administered endotracheally can be just as effective. Sodium bicarbonate 100 mmol IV is administered empirically.

- If ventricular fibrillation develops, immediately defibrillate with 400 J and proceed as described in table 3.5.5.

- As soon as a central pulse is detected, do a blood gas and electrolyte estimation and correct any deficiencies.

If there is still no reaction, 5-10 mL of a 10% calcium chloride solution is administered IV. The administratioon of all these preparations is an attempt to convert asystole into ventricular or fine fibrillation into coarse fibrillation to make defibrillation possible.

Inotropic agents are administered as necessary:

Dobutamine HCl (dobutrex)

Dopamine HCl (intropin)

Isoproterenol HCl.

Detailed Discussion

Oxygen Administration

Oxygen should be supplemented during CPR. *Hypoxia during CPR is the result of the low cardiac output (and the large oxygen difference arteriovenously). This is associated with external chest compression, intrapulmonary shunting and ventilation-perfusion abnormalities.* The alveolar and arterial oxygen tension differ, with the result that hypoxaemia develops. Hypoxaemia during CPR produces a significant metabolic acidosis (as a result of poor cardiac output and anaerobic metabolism). This often diminishes the effects of chemical and electrical therapy. Inhalation of oxygen can reduce both the magnitude and the extent of ST-segment changes on ECG in patients with acute myocardial infarction. The trauma/shocked patient is hypoxaemic due to various reasons, i.e. ventilatory perfusion mismatching. *Therefore 100% inspired oxygen should be used during resuscitation.*

Ventilatory Adjuncts

A most important requisite for successful resuscitation is ensuring adequate ventilation by intubation and mechanical ventilation.

Bag Valve Mask Ventilation with 100% Oxygen

A bag-valve device can initially be effectively used with a well-fitting mask to ensure adequate ventilation, provided that the nasopharynx is clear. It is correct practice to oxygenate the patient with a ventilation mask or bag-valve device preceding endotracheal intubation, as immediate hyperventilation with a mask in the presence of adequate cardiac compression ensures essential tissue oxygenation, allowing time for the endotracheal intubation procedure. The correct use of a bag-valve device depends on a proper mask fit and a patent airway. *The airway can be kept open using an oropharyngeal airway as this type of patient is obviously unconscious. It should not be used in a conscious patient where the gag or swallowing reflex is present, as vomiting or laryngospasm may result.*

It is essential that the correct size oropharyngeal tube be inserted. If it is too small, the device may press against the back of the tongue thereby displacing the tongue posteriorly, aggravating airway obstruction. If it is too large, the device may press against the posterior pharyngeal wall, again aggravating airway obstruction. *A rule of thumb commonly used is to measure the distance from the angle of the mouth to the earlobe choosing an oropharyngeal airway of similar length.*

Satisfactory oxygenation can be achieved by this simple method. *However, in the absence of a protected airway, adequate lung inflations may require high pharyngeal pressures, leading to gastric distention which promotes regurgitation with the potential for aspiration of gastric contents. This also elevates the diaphragm interfering with adequate lung inflation. It is important therefore that the trachea be intubated as soon as practicably possible during the course of resuscitation without interfering with the resuscitation attempt.*

Prior to intubation it is necessary to synchronize chest compressions and ventilation to a ratio of 5:1 and with a slight pause before ventilation to prevent gastric distention.

Endotracheal Intubation

With endotracheal intubation the maximum interruption of ventilation should not exceed 30 seconds. Repeated attempts at intubation, which interferes with oxygenation of the patient, must be avoided. Adequate ventilation and oxygenation with 100% oxygen must be provided between attempts to intubate. A range of tube sizes must always be available, with a view to passing the largest tube which will comfortably pass through the vocal cords (*a tube which is too narrow may significantly increase airway resistance*). When intubating children, it must be borne in mind that the narrowest part of the trachea is at the level of the cricoid cartilage. *Cuffed tubes should only be used in adults and in children over the age of 8 years.*

Either an oral or a nasal tube can be used although the latter is preferred for aftercare.

A rule-of-thumb for choosing approximate *oral tube size (internal diameter)* is as follows:

Premature infants - 3.0 mm ± 0.5 mm

0-6 years - 3.5 mm / age (yrs)/3

7-12 years - 4.5 mm + age (yrs)/4

Adult female - 8.0 mm ± 0.5 mm

Adult male - 9.09 mm ± 0.5 mm

A nasal tube would be 0.5 mm smaller (an alternative approximate guide is to choose a tube size having a diameter similar to the patient's little finger).

Correct endotracheal tube length should preferably be measured prior to intubation. Too short a tube may well slip out of the trachea if the patient's head is moved. Too long a tube may come to lie in the right (rarely the left) main bronchus, with inadequate ventilation of the opposite lung.

A rule-of-thumb in choosing the appropriate oral tube length is as follows:

Premature infants - 9 cm

0-6 months - 10 cm

6-12 months old - 11 cm

≥ 1 year old - 12 cm + age (yrs)/2

≥ 3 years old - Measure the distance from the corner of the mouth to the earlobe and add on half of that distance.

Nasal tube length can be determined by measuring the distance from the corner of the nose to the earlobe plus the same distance.

Whenever possible an assistant should apply pressure to the anterolateral aspects of the cricoid cartilage using his thumb and index finger while intubation is attempted (Sellicks manoeuvre). The pressure is to be maintained until the endotracheal tube is correctly in position and the cuff has been inflated. Any intubation attempt must never take longer than 30 seconds. If unsuccessful, remove the tube and ventilate the patient well with 100% oxygen before reattempting the procedure.

Once an endotracheal tube is in place, ventilation is continued. Ventilation need not be synchronized with chest compressions but should be performed asynchronously at 12 to 15 ventilations per minute, which is the equivalent of one ventilation to five compressions.

Mechanical Ventilation

The patient should be connected to an automatic (volume-cycled) ventilator as soon as possible. Pressure-cycled automatic ventilators should never be used during CPR because chest compressions terminate the inspiratory cycle, resulting in inadequate ventilation.

Circulatory Adjuncts

External Cardiac Compressions (Closed Cardiopulmonary Resuscitation - CCPR)

Once cardiac arrest has been diagnosed, properly performed external compressions are started. The external chest compression technique consists of serial rhythmic applications of pressure over the lower half of the sternum. These compressions provide circulation to the heart, lungs, brain and othger organs as a result of a generalized increase in intrathoracic pressure and/or direct compression of the heart. Blood circulated to the lungs in this way will be sufficiently oxygenated to maintain life if the compressions are accompanied by proper ventilation of the patient.

Technique

The heel of one hand is placed two fingerbreadths above the lower end of the xiphisternum. The other hand is placed on top of the hand already on the sternum, so that all fingers are pointing laterally in the same direction, but with the fingers lifted off the chest wall. Compression is applied with the heel of the hand placed on the sternum in the midline. The sternum must be pushed down 3.0 to 5.0 cm for an average-sized adult, the pressure released completely and the chest wall allowed to return to normal. However, the hands should not be lifted from the chest wall or the position changed in any way. Relaxation time and compression time should be equal. The sternum is compressed at a rate of 80-100/minute and ventilation is given after every fifth compression. (There should be a slight pause for ventilation if the patient is not yet intubated).

Physiology of Circulation with External Compressions

Two theories are supported:

Cardiac Pump Theory

The cardiac pump theory is based on the belief that external chest compression of the heart results in direct compression of the heart between the sternum and the spine, with an increase in pressure within the ventricles and closure of the mitral and tricuspid valves. The pressure was thought to move blood into the pulmonary artery and the aorta. This theory is supported by studies that demonstrate higher stroke volume and coronary flow with high-impulse (moderate force and brief duration) external chest compression at high rates.

Thoracic Pump Theory

The "conventional theory" or "cardiac pump theory" has been challenged by supporters of the thoracic pump theory. The latter contends that an increase in intrathoracic pressure

(resulting from external compression) causes an equal transmission of pressure to all intrathoracic vascular structures. However, since arteries resist collapse, due to increased internal pressure, virtually all pressure is transmitted from the intrathoracic to the extrathoracic arteries. However, full pressure transmission does not occur. This is attributed to venous collapse and competent venous valves.

With the method used here, the chest wall is compressed and there is thus a generalized increase in intrathoracic pressure, affecting all structures equally. The heart acts only as a passive conduit when the chest wall is compressed, with a resultant antegrade flow through the left ventricle as a result of the movement of blood out of the pulmonary circulation and through open mitral and aortic valves.

Although there is no pressure gradient between intrathoracic vessels during closed chest compressions, a gradient is created between the intrathoracic and the extrathoracic vascular systems. Retrograde flow in the thorax is prevented by the collapse of the intrathoracic veins, partial closure of the pulmonary valve, and compression of the ventricular outflow tract. Retrograde flow is further prevented by competent venous valves at the thoracic outlet. Venous return to the heart is said to be principally from the superior vena cava and there is virtually no flow to the heart from the inferior vena cava. *Therefore blood flow is caused by an extrathoracic arteriovenous pressure gradient.*

The thoracic pump theory is supported by the following:

- Chest compressions on a patient with a flail chest do not produce an increased arterial pressure unless the chest is stabilized with a belt which allows for an increase in intrathoracic pressure.

- It has been observed that patients who sustain a cardiac arrest and who were able to cough vigorously prior to imminent losing of consciousness, were able to remain conscious, and that the systolic arterial pressure during coughing is higher than 100 mm Hg. This significant increase in intrathoracic pressure thus provided cerebral blood flow.

- Two dimensional echocardiography shows that the heart is a pressure conduit rather than a pump during CPR. This is because the mitral and tricuspid valves remain open during chest compressions.

Recognition of the thoracic pump mechanism has led to important research in techniques to improve closed chest artificial perfusion by enhancing intrathoracic pressure. Experimental techniques include simultaneous ventilation and compression (SVC-CPR), or the addition of an abdominal pump as in interposed abdominal compression CPR (IAC-CPR), or increasing venous preload by means of MAST application and intravascular volume loading.

The thoracic pump generates a cardiac output of 25% of normal. This inefficiency is portrayed by the following data during CCPR: myocardial capillary and coronary perfusion is 1-5% of normal, cerebral blood flow is 3-15% of normal if CCPR is begun immediately at the time of arrest and brain blood flow decreases with time. As CCPR continues, the intracranial pressure becomes elevated because of the high venous pressures associated with

thoracic compressions. This results in a shunting of carotid blood flow to the face instead of to the brain. Measurement of carotid blood flow would thus provide a grossly inaccurate indication of the cerebral blood flow. Most important is that even short delays in the initiation of CCPR after cardiac arrest result in a marked decrease in brain perfusion; a delay of 5 minutes results in no detectable brain perfusion.

Techniques such as SVC-CPR and IAC-CPR produce some enhancement of brain perfusion, but neither compare well to the near-normal cardiac output, myocardial blood flow and brain perfusion produced by open chest cardiac massage.

Some investigators showed a decreased survival rate when SCV-CPR and abodominal binding was used, and an increased survival rate with open chest CPR. Experimental open chest cardiac massage for 30 minutes following a 4 minute cardiac arrest resulted in a normal neurological outcome. Both CCPR and SVC-CPR resulted in brain-dead animals in the same study. Studies of expansion of intravascular volume during CPR suggest worsening of the haemodynamic and perfusion parameters.

It has been shown that CCPR provides some protection only if started immediately and followed by definitive resuscitation within 6-18 minutes. Large clinical studies of the effectiveness of closed cardiac compression uniformly suggest that it is effective for only 4 minutes to 6 minutes in enhancing either resuscitation or chances of survival.

Since there is no conclusive evidence at present that the use of any of the above mentioned "new" techniques during resuscitation improves survival of the cardiac arrest victim, their routine use therefore is not recommended except fot the application of the MAST if hypovolaemia is considered to be a cause or a contributing factor. *The military anti-shock garment (MAST) has been shown to have a haemostatic effect, minimizing bleeding under the suit and it is a method for challenging the central circulation with a volume load.* If the patient's haemodynamic status improves clinically when the garment is inflated, then it should remain inflated until adequate volume has been replaced, at which time it should be gradually deflated. If the patient's condition worsens with inflation, the garment should be deflated immediately with prompt redistribution of augmented central volume.

Intra-Aortic Balloon Counterpulsation

This adjunct consists of a balloon, inflated in the aorta synchronously with left ventricular contraction to ensure increased aortic pressure and improved coronary artery filling. *One use of this device is in left ventricular pump failure that occurs in the low-output syndrome and in patients with acute myocardial infarction when they go into shock. It is particularly important in the management of these patients until it can be established (by cardiac catheterization) whether the condition is surgically treatable.* This technique only improves the prognosis if a surgically correctable lesion is present. There is no documented evidence that this device has a beneficial effect on survival of cardiac arrest victims.

Open-Chest CPR (Internal Cardiac Compressions)

Open-chest CPR provides superior haemodynamics and a significantly improved cardiac output and myocardial and cerebral blood flow. It produces a neurological outcome

markedly better than either CCPR or SVC-CPR in animal studies.

When performed correctly, this technique may provide near-normal perfusion to the brain and heart. *Only those experienced in carrying out thoracotomy and respiratory support should apply open-chest cardiac compression. Its indications are limited but may include cardiac arrest associated with trauma especially penetrating chest trauma and injuries of the chest. It is mandatory in patients with cardiac arrest due to penetrating cardiac injuries and cardiac tamponade.*

Intravenous Access

A peripheral line and a central line should be inserted as soon as possible for the administration of drugs and CVP monitoring. Wide-bore cannulae should be inserted for the rapid administration of fluids and blood in the hypovolaemic patient. Placement of the central line should not interfere with cardiac massage.

If no intravenous access is available, drugs such as adrenaline, atropine and lignocaine can be instilled into the endotracheal tube, where they are rapidly absorbed by the circulation via the lungs.

The administration of drugs via the intracardiac route should be avoided if possible. Coronary vessel rupture, myocardial damage, pericardial tamponade, haemomediastinum and tension pneumothorax are just some of the formidable complications of this procedure. *Only if both an intravenous line and an endotracheal tube are not available should intracardiac adrenaline be given. One must ensure that the needle is in a cardiac chamber by withdrawing blood into the syringe before injecting the adrenaline, as myocardial necrosis results if adrenaline is injected directly into the heart muscle.*

Electrical Therapy (Defibrillation)

In ventricular fibrillation, the sooner the patient is defibrillated, the greater is the chance of successful cardioversion. On starting life-support measures (A = airway, B = breathing, C = circulation), a defibrillator should be called for immediately (D = defibrillator).

Method for Defibrillation

Confirming the absence of a pulse, with or without monitor evidence of ventricular fibrillation. Defibrillation (asynchronized) in an adult is indicated at 100-200 J, initially. After this the patient is checked for a return of pulse. If no pulse returns, defibrillation is repeated with approximately 300 J and the pulse rechecked. If still not pulse is detected, defibrillation is performed with 360-400 J and the pulse rechecked. Subsequent defibrillations, especially if higher energy levels are used, may cause structural myocardial damage and therefore should not exceed 400 J. (*In children, the energy requirement is 2 J/kg initially increasing to 4 J/kg if no pulse returns*). The ideal paddle size for adults is a 10 cm in diameter, and for children approximatelyh 5 cm in diameter.

If after successful defibrillation the patient relapses into ventricular fibrillation, defibrillation is repeated, using the same amount of energy that was required to successfully

cardiovert the patient previously. The most significant factor in good resuscitation results is the timing of defibrillation - early defibrillation saves lives. Moreover, there is evidence that defibrillation is the single most effective intervention for converting ventricular fibrillation to another rhythm.

Initial management should be designed to provide immediate CPR with great emphasis placed on early defibrillation. If the cardiac monitor confirms cardiac arrest due to asystole, defibrillation is immediately performed using 360-400 J.

In cases of internal cardiac massage (open chest), defibrillation can be applied directly onto the surface of the heart using small "internal paddles", defibrillating at 5 J initially, increasing the energy stepwise, if necessary, to a maximum of 50 J.

The following is suggested for paddle placement:

- Paddle position: Slightly to the right of the sternum, below the right clavicle and just lateral and inferior to the apex, in the midaxillary line.

- Paddle pressure: Firm pressure to be applied.

- Electrode paste: *Only ECG paste or saline soaked swabs are to be used. Any TNT paste present should be wiped off before defibrillation. (No KY-jells, alcohol swabs or sonar gels).*

Drug Therapy

Ventricular Fibrillation

Adrenaline Administration

As was mentioned before, defibrillation is the first step in the treatment of this lethal rhythm disturbance, but drug therapy is indicated to improve cardiac output and blood pressure. If no pulse/rhythm returns, CPR is continued and adrenaline is administered intravenously (or via the endotracheal tube).

The 1 mL 1:1000 solution should ideally, if time allows, be diluted with 9 mL of sterile water or saline to form a 1:10000 solution. In adults 5-10 mL of this solution is administered, and in children the dosage is 0.1 mL/kg of the 1:10000 solution. The dose of adrenaline can be repeated every 5 minutes during CPR if there is no response, and defibrillation should be performed 1 minute after each dose.

The rationale for the use of this agent in cardiac arrest has changed. Earlier it was suggested that this agent would induce electrical and mechanical activity in the asystolic heart. A recent study on the effects of adrenaline in the resuscitation of patients in asystole demonstrated no greater rate of rhythm change with the administration of adrenaline than with the administration of sodium bicarbonate. There is little evidence other than clinical experience that adrenaline alone is of value in converting asystole to any other rhythm during closed-chest massage, although this agent does convert electrically "fine" ventricular

fibrillation to "coarse" fibrillation in the laboratory. There is controversy about whether this enhances the success rate of defibrillation.

Its potential adverse beta adrenergic effects during cardiac arrest include increased myocardial membrane calcium conduction, myocardial wall tension, myocardial oxygen consumption due to increased myocardial work, endocardial flow resistance and reduced subendocardial perfusion, while decreasing peripheral vascular resistance.

The alpha adrenergic effects of adrenaline, however, do make it useful in resuscitation. The alpha adrenergic properties of adrenaline result in a valuable redistribution of perfusion during closed cardiac massage. It increases aortic diastolic pressure, coronary artery blood flow and cerebral blood flow during conventional CPR. Aortic diastolic pressures above 30 mm Hg correlate with increased resuscitability in dogs. The dose of adrenaline currently recommended in ACLS protocols may not be adequate to achieve adequately raised aortic pressures.

A retrospective study in the prehospital setting showed no difference in successful resuscitation between those who received adrenaline and those who did not. The dose of adrenaline needed in dogs to elevate the aortic diastolic pressure to the appropriate level is 10 to 20 times that currently recommended in humans.

Other workers continue to believe that beta stimulation is beneficial, increasing inotropy and coarsening "fine" ventricular fibrillation.

Lignocaine Administration

If there is no response to the initial adrenaline dose, lignocaine must be administered intravenously or via the endotracheal tube as a bolus of 1 mg/kg initially. Ventilation and cardiac compressions should continue, with defibrillation approximately one minute later if the pulse is not palpable.

Thereafter constant infusion of lignocaine at 2 to 4 mg/minute is recommended. As protection against arrhythmias lignocaine administration reduces the incidence of primary ventricular fibrillation by raising the ventricular fibrillation threshold and lowering the excitability of ischaemic myocardial tissue.

Bretylium Tosylate Administration

If there is no response to initial adrenaline and lignocaine administration bretylium tosylate is administered at a dose of 5 mg/kg initially. Ventilation and chest compressions are continued, and the patient is defibrillated approximately one minute later. If no pulse returns, CPR is continued and the bretylium tosylate is repeated every 15 minutes at a dose of 10 mg/kg until a total dose of 30 mg/kg has been given if necessary. Defibrillation attempts should be repeated after each dose of bretylium tosylate.

Bretylium tosylate can be used to treat persistent ventricular fibrillation, although it cannot be used as first-line therapy. It first releases catecholamines, followed by a postganglionic adrenergic blocking action, which often brings about hypotension. It acts

directly on the myocardium and interferes with autoregulation of the adrenergic effects of the sympathetic nervous system. Its effects include inotropy, prolonging the action potential and refractory period of the purkinje fibres, and it raises the ventricular threshold. This preparation is also believed to inhibit the fibrillation caused by hypokalaemia and hypothermia, although its antifibrillating effect has recently been challenged.

Dobutamine Hydrochloride Administration

Following successful resuscitation the ischaemic myocardium invariably causes hypotension due to reduced cardiac output. The administration of dobutamine HCl may be valuable in this situation. The dosage is 2.5-10 microg/kg/min. This preparation has selective beta-adrenergic stimulating properties that increase myocardial contractility. It also reduces preload and afterload due to vasodilatation. The resultant effects are increased cardiac output and haemodynamic indices on left ventricular function without a noticeable effect on blood pressure and it has minimal chronotropic effects (heart rate is minimally increased). It may, however, exacerbate myocardial ischaemia.

Sodium Bicarbonate Administration

If there is no response to initial adrenaline, lignocaine and bretylium tosylate administration, or if the arterial blood-gas analyses indicate metabolic acidosis, sodium bicarbonate at a dose of 1 mmol/kg should be given IV, followed by 0.5 mmol/kg IV every 10 minutes during CPR. However, the mainstay of the control of acid-base balance in cardiac arrest is ensuring adequate alveolar ventilation. Hyperventilation removes carbon dioxide, which is freely diffusable across the cellular membranes. It is important tonote that there is very little evidence that the administration of sodium bicarbonate improves the outcome of cardiac arrest. Systemic metabolic acidosis develops rapidly during perfusion arrest which is not well-reversed by conventional CPR. A multiplicity of variables affect this parameter, including duration of arrest, adequacy of CPR, haemoglobin levels and underlying abnormalities, i.e. chronic obstructive lung disease.

Adverse effects of continued acidosis during resuscitation may include: depression of myocardial contractility, increased pulmonary vascular resistance, increased ventricular fibrillation threshold and decreased response to catecholamines. Higher doses therefore are required in the presence of acidosis. It has been shown that the success rate of defibrillation is not significantly affected by variations in the pH level.

Controlled hyperventilation should always be the first measure used to counteract tissue acidosis during cardiac arrest.

Excessive administration of sodium bicarbonate during resuscitation results in impaired oxygen release from haemoglobin (oxygen dissociation curve shifts to the left), reduced ionized (effective) to non-ionized calcium ration, a potassium shift from serum into cells, ventricular tachycardia and fibrillation, and sustained cardiac contraction ("stone heart"), and it may also be injurious by producting hypervolaemia and hyperosmolality.

During CPR, less sodium bicarbonate is needed than was previously assumed, whereas more is needed after restoration of spontaneous circulation when washout of acids occurs. If

CPR is commenced early, within 2-5 minutes, and lasts for less than 10 minutes, the acidaemia can usually be corrected by hyperventilation alone. During sodium bicarbonate administration, more hyperventilation is needed to eliminate carbon dioxide released by the administered sodium bicarbonate. Without hyperventilation, sodium bicarbonate, which raises serum pH may paradoxically lower brain pH, because carbon dioxide passes through the blood-brain barrier more readily than the charged bicarbonate or hydrogen ions and thereby worsens cerebral acidosis and probably tissue acidosis. Therefore, sodium bicarbonate should not be administered routinely in cardiac arrest, but a dose of 1 mmol/kg IV can be given when the suspected arrest period was longer than 2-5 minutes (prior to commencement of CPR), or when CPR has continued for longer than 10 minutes without effect. Subsequent doses should be guided by arterial pH measurements, aiming for values approaching 7.4.

Immediately after restoration of spontaneous circulation, the release of large amounts of acid (lactic and carbonic acid) from tissue cells calls for increased controlled hyperventilation and possibly for IV sodium bicarbonate administration, titrated according to calculated base deficits (using the formula: (BE x Wt x O.3)/3.

Continuous adjustments of ventilatory volumes is required to maintain a $PaCO_2$ of between 20-35 mm Hg, with the use of sodium bicarbonate solely to correct base deficit to within 5 mmol/L, aiming for an arterial pH of 7.3-7.35 and a base deficit of less than 5 mmol/L.

Alkalosis has significant adverse effecxts, and there is data indicating that sodium bicarbonate shifts the oxyhaemoglobin dissociation curve to the left, inhibiting the release of oxygen. Sodium bicarbonate also induces hyperosmolality and hypernatraemia: it produces paradoxical cerebral and myocardial acidosis due to an increased production of carbon dioxide, which is freely diffusable into the cerebral and myocardial cells (this depresses the function of the bran and the myocardium), especially the ischaemic myocardium); it induces adverse effects due to extracellular alkalosis and it may inactivate the effects of administered catecholamines and inotropes. Sodium bicarbonate therefore is not a first line drug, but should only be administered, if defibrillation, cardiac compression, adequate ventilatory support and drug therapy have failed, or with laboratory evidence of metabolic acidosis. Empiric administration in patients with cardiac arrest lasting longer than 2-5 minutes prior to commencement of CPR seems reasonable though.

Factors predisposing to ventricular fibrillation and refractory cardiac arrest, such as myocardial ischaemia, hypoxia, acidosis, electrolyte abnormalities (especially K+) and/or hypothermia must always be borne in mind and managed appropriately.

Asystole

This condition is recognized by a straight line on the cardiac monitor together with the absence of a palpable central pulse. CPR is started immediately.

Defibrillation

The patient is defibrillated using 400 J if no pulse is palpable. Defibrillation is effective in ventricular fibrillation but has no effect on the heart in asystole. However, it is

done on account of the possibility that a very fine ventricular fibrillation may mimic asystole.

Drug Therapy

Adrenaline

Defibrillation is followed by the insertion of an IV line and the administration of 1 mg adrenaline intravenously or via the endotracheal tube. The dose is repeated every 5 minutes as necessary. The aim is to elicit a rhythm which could be further treated. The details of its administration are as described for ventricular fibrillation.

Atropine Sulphate

If there is no response to the above, atropine sulphate is administered at a dose of 1 mg for adults (0.02 mg/kg for children with a minimum initial dose of 0.1 mg) and is rapidly administered intravenously or via an endotracheal tube. This dose is repeated after 5 minutes. The maximum total dose is 2 mg in adults and 1 mg in children.

The action of atropine is anticholinergic and is rate-dependent. Rapid administration blocks the vagal effect (vagolytic), and slow administration has a paradoxical central vagotonic effect which slows the heart rate. There is data to suggest its efficacy in the treatment of ventricular asystole. However, it may exacerbate the ischaemia or increase the size of an infarct due to increased cardiac work.

Sodium Bicarbonate

If there is still no response or if asystole has been present for longer than 5 minutes, sodium bicarbonate at a dose of 1 mmol/kg intravenously must be administered and followed by 0.5 mmol/kg every ten minutes during CPR. Never administer sodium bicarbonate via an endotracheal tube.

Inotropic Agents

Dobutamine hydrochloride (2.5-10 microg/kg/min), dopamine hydrochloride (0.5-1.0 microg/kg/min) and/or isoproterenol hydrochloride (0.05-0.3 microg/kg/min) can be considered.

Calcium in Resuscitation

In perfusion arrest anaerobic metabolism and adenosine triphosphate (ATP) depletion ensue. Within 5 minutes of the onset of perfusion arrest, ATP reserves in the brain are zero, and are reduced by 40% in the myocardium. Organs with significant glucose or glycogen stores support residual ATP levels by anaerobic metabolism. However, there is no such option for the brain which does not have such stores. Perfusion arrest causes cell death. Large ionic gradients across the cell membrane decay rapidly, i.e. Ca++ (10000:1), Na+ (140:5) and K+ (4:130). Potassium concentration in the interstitial fluid is raised as Ca++ nears equilibrium with intracellular fluid. These shifts also occur in the myocardium. Cellular Ca++ overloading due to ischaemia occurs in the myocardium and arterial walls.

ATP is metabolized to adenosine, which diffuses into the interstitial fluid and serves as a powerful vasodilator. Thus peripheral vascular resistance may be reduced and intravascular volume inadequate for support of perfusion following cardiac arrest (relative hypovolaemia). This relative hypovolaemia may in part account for the poor results achieved in the past with conventional CPR in generating brain perfusion when the institution of CPR has been delayed for even 1 to 2 minutes.

As was pointed out, ischaemia results in cellular Ca++ overloading in the myofibril of both the myocardium and arterial walls and although the administration of calcium increases myocardial contractility it can also cause coronary vasospasm and increase myocardial irritability. The usefulness of calcium in resuscitation is limited and it may even be contraindicated. It has a place only as a last resort during the resuscitation of cardiac arrest not responding to routine treatment. This is supported by evidence that calcium channel blockers preserve the myocardium and brain cells if administered early after cardiac arrest. Recent studies found no benefit from calcium administration during advanced resuscitation attempts. High calcium levels may be detrimental to the myocardium, and is dangerous in the presence of hypokalaemia. It is evident from the above-mentioned that calcium administration should be excluded from the routine protocol for the initial management of cardiac arrest, but it can still be tried if all other methods have failed.

The preferred compound is calcium chloride (10% solution), given in a dose of 2-4 mg/kg slowly IV and repeated if necessary at 10 minute intervals. The alternative compound is calcium gluconate given in a dose of 10 mL IV. It should always be ensured that the infusion is free-flowing, and calcium should never be administered via an endotracheal tube.

Calcium is indicated in patients with hyperkalaemia, hypermagnasaemia, hypocalcaemia (i.e. following massive blood transfusion) and with calcium channel blocker toxicity.

Calcium Channel Blockers

In the setting of cardiac arrest, calcium channel blockers may have beneficial effects:

- Preservation of the myocardium (protection by pretreatment).

- Reduced vulnerability to ventricular fibrillation.

- Cerebral protection against hypoxic ischaemic damage.

These agents may also have significant preventative potential as well as clinically unexplored therapeutic potential in sudden cardiac death. None of these, however, have yet been shown to be of unequivocal benefit in the management of cardiac arrest, and much more research will be needed to clarify the use of calcium channel blockers in attempts to restore spontaneous circulation following cardiac arrest.

Verapamil is the only intravenous caclium channel blocker preparation available in this country. Nifedipine is only available as an oral preparation. The use of calcium channel blockers following cardiad arrest, seems atractive on account of their multiple beneficial

effects. However, they also have hazardous cardiovascular effects. The dangerous effects include:

- Dose-dependant slowing of the conduction system (A-V block) with possible cardiac arrest (particularly with verapamil).

- Vasodilatation with hypotension (particularly with nifedipine).

- Negative inotropic effect (perhaps more with nifedipine).

The effects on cerebral and myocardial ischaemia are not yet well documented. The administration of calcium channel blockers has been successful in preventing cerebral arterial spasm and thus the no-reflow phenomenon. This phenomena consists of hyperaemia during the first 5 minutes of reperfusion followed by a progressive and prolonged decline in cerebral blood flow. It has been shown that after 20 minutes of brain ischaemia and 60 minutes of reperfusion, flow is only 20% of normal. This phenomenon is not related to increased intracranial pressure and occurs despite adequate perfusion pressures. Preservation of normal cerebral perfusion after resuscitation was reported in dogs treated following 20 minute perfusion arrest with any of several calcium channel blockers, for example, verapamil, magnesium sulphate and lidoflazine. Studies have demonstrated a role of calcium channel blockers in the management of post-arrest encephalopathy in animals.

Following cardiac arrest lasting up to 10 minutes, administration of calcium channel blockers to laboratory animals was effective in ameliorating the hypoperfusion syndrome in the brain as well as brain tissue calcium overload and neurological deficits.

This suggests that late calcium overloading may occur because of direct increases in membrane permeability rather than through specific calcium channels. A similar no-reflow phenomenon occurs in the ischaemic heart and liver.

Free Radical Scavengers

The possible use of free radical scavengers in brain resuscitation after cardiac arrest is presently being investigated. It is believed that reperfusion injury (no-flow phenomena) starts with free iron-triggered oxygen and hydroxyl radical which, concomitant with calcium loading of mitochondria, create chemical reactions leading to membrane damage and cell death.

There is evidence to support the combined roles of fero-feri triggered oxygen and hydroxyl accumulation and calcium in lipid peroxidation.

The calcium-triggered formation of arachidonic acid during reperfusion leads to formation of vasoactive agents (prostaglandins, thromboxane and leukotriens) which might worsen the microcirculation and thus cause reperfusion failure and reperfusion injury. The role played by free radicals in the cell-necrotizing process is, as yet, uncertain.

Hypovolaemic Cardiac Arrest

Pharmacologic intervention in the hypovolaemic patient with cardiac arrest does not differ significantly from the non-hypovolaemic patient. It is an absolute priority, however, to restore blood volume in the patient. Cardiopulmonary resuscitation with ventilation and external heart massage must be continued. Rapid fluid replacement should be effected through two or more wide-bore needles in peripheral veins as well as one centrally-placed catheter. As many as four or more infusions may be required to ensure satisfactory volume replacement. An effective method of administering large quantities of fluid is to do a cut-down on the *v. basilica* or on the *v. saphena* (proximally) and to insert a polythene tube from a sterile intravenous infusion set. A sterile paediatric feeding tube can also be used as an intravenous catheter. Cut-downs can, however, be time-consuming. A MAST suit may remove the necessity for a *v. saphena* cutdown. A central venous catheter with a wide lumen is the quickest method of administering large volumes of fluid. The standard catheter used for central venous cannulation is a number 16 "intra-cath". These catheters deliver less than half of the flow rate of a standard no 16 needle introduced into a peripheral vein! This type of central catheter should only be used for fluid monitoring purposes. A rapid flow can best be achieved by introducing a broad lumen catheter into the subclavian vein. Different types of short and broad lumen catheters (8.5 FR) for central placing are available. The advantages are that they provide a rapid flow and a rapid method of percutaneous placement without requiring cut-down. An even faster flow is possible if infusion sets with short tubes are used. The administration of fluid can also be speeded up by using a pressure pack around the plastic vaculitre. This is more effective than a hand pump.

It is necessary to have warmed crystalloids (37-40 °C) available for administration and blood should be prewarmed before it is given, as hypothermia can have serious adverse effects.

Mild hypothermia results in increased oxygen consumption, increased haemoglobin oxygen affinity, potassium leakage, platelet sequestrationand suppressed coagulation. As bank blood is deficient in coagulation factors and platelets it is preferable to give a unit of fresh frozen plasma after every fourth unit of bank blood. Platelet concentrate should be administered after every fifth unit of bank blood. The warming of blood reduces its viscosity and allows the blood to flow more quickly. The most important consideration is the rapid administration of large volumes of warmed Ringer's lactate and blood while CPR is continued without interruption.

A pneumatic pressure suit (MAST) can be used for its haemostatic effect. It also increases the peripheral resistance. Its use is contra-indicated in patients with cardiac and thoracic vascular injuries. In these injuries it causes secondary exsanguinating haemorrhage associated with increasing blood pressure.

MAST, to a large extent, also controls intraabdominal bleeding and can obviate the need for laparotomy and aorta clamping in the emergency unit; the latter can usually be done more effectively in the operating theatre. Laparotomy for severe abdominal bleeding has an extremely high mortality when carried out in the emergency unit. It must be remembered, however, that MAST is no substitute for massive volume replacement! In patients with chest injuries, external heart massage is sometimes ineffective or even impossible, i.e. with a flail

chest or cardiac tamponade. Inthese cases emergency thoracotomy and internal heart massage is the only expedient option.

To ensure successful resuscitation all bleeding must be controlled. Any conditions which restricts the ability of the patient to ventilate or perfuse must be eliminated. An emergency thoracotomy is sometimes the only method of achieving this.

The indications for an emergency thoracotomy are:

- Cardiac tamponade

- Traumatic cardiac arrest

- Penetrating cardiac injury

- Continued massive intrathoracic haemorrhaging (more than 1500 mL blood obtained with the introduction of an intercostal drainage tube, or continued blood loss of 200 mL per hour over 3 to 4 hours)

- Extensive thoracic blood-vessel injury

- Continued air leakage

- Oesophageal injury

- Diaphragmatic injury

- Severe cardiac tamponade requires immediate thoracotomy.

The signs of tamponade include the following:

- severe shock

- low pulse pressure

- engorged neck veins

- soft heart sounds

- dramatically raised central venous pressure

- positive pericardiocentesis - this has diagnostic and therapeutic value.

Pericardiocentesis is carried out under sterile conditions with the thorax of the patient raised to 30 degrees. A large syringe with a number 18 spinal needle connected to the V lead of the electrocardiograph by a "crocodile clamp" is used. The four limb leads of the ECG are attached to the patient. Entry is through the right costosternal angle. The needle is advanced cautiously in the direction of the left shoulder.

Continuous suction is applied to the syringe. A "pop" is often heard as the needle perforates the pericardium. Aspiration of unclotted blood is diagnostic of haemopericardium. Alternatively the needle can be inserted to the left of xiphisternum and pushed in the direction of the right shoulder. If the ECG at any time shows an injury pattern, the needle is then withdrawn immediately.

Injured patients with cardiac shock usually require intubation and ventilation. It is important to recognize the presence of a tension pneumothorax. Displacement of the trachea with contralateral and absence of respiratory sounds is suggestive of this condition. The drain is inserted through the fourth intercostal space in the midaxillary line. Continued air leakage and blood loss will lead to suppressed respiration and hypovolaemic shock and, if present, a thoracostomy must be considered.

Cardiac Arrest in Anaphylaxis (Vasodilation)

Anaphylaxis is an example of this type of cardiac arrest. Pharmacological and electrical intervention is the same as for normovolaemic patients with the early administration of intravenous adrenaline being a priority. Rapid volume administration to overcome the relative hypovolaemia effects of vessel dilatation is necessary. Further measures are aimed at the management of cardiac arrest (VF or asystole) and the stabilization of the cardiovascular and respiratory status as already outlined.

Summary

Cardiac arrest requires recognition of its mechanisms, determination of the aetiological factors and immediate and organized management in a co-ordinated and appropriate sequence.

Comment

Cardiac Arrest

K. D. Boffard

A cardiac arrest in the traumatised patient is the final occurrence in a progression of events which began with the initial injury. Unless the progression can be reversed before cardiac arrest takes place, it is very unlikely that resuscitation will be successful after the arrest has occurred.

In trauma, the two circumstances to be considered are:

- Hypovolaemic cardiac arrest

- Myocardial contusion

All patients must be oxygenated early and adequately.

Hypovolaemic (Ischaemic) Cardiac Arrest

The overriding requirement in hypovolaemia is to restore the circulating blood volume before cardiac arrrest occurs.

Medical Anti-Shock Trousers (MAST)

Also known as the pneumatic antishock garment (PASG), this consists of three inflatable compartments, one for each leg the function of which is both to tamponade bleeding and to treat hypovolaemic shock, and an abdominal compartment, in which the primary function is to tamponade abdominal bleeding. Only the anterior part of the abdominal compartment inflates. The posterior part is sealed toprevent movement in the case of lumbar spine injury.

The MAST is said to work as follows:

- Act as a splint

- Tamponade any venous bleeding either in the limbs or abdominal cavity

- Shunt blood to the upper half of the body from the lower half, by increasing peripheral resistance in the legs. This may in itself make it much easier to insert peripheral IV lines.

- Provide a small amount of autotransfusion. This is probably not significant (+/- 250 mL), since at the time the MAST is likely to be applied, the patient will be vasoconstricted, and there will be a minimum of pooling of blood in the legs.

While recent data suggests that the MAST does not improve overall survival, especially in those patients whose transport time to hospital is less than 15 minutes, it is most useful in the temporary elevation of blood pressure until adequate IV fluids can be provided, and is specifically helpful under the following circumstances:

- Fractured pelvis: The MAST is extremely useful in the stabilisation of the pelvis, the tamponading of pelvic bleeding, and transport of patients with pelvic fractures.

- Post-partum haemorrhage: The use of the MAST will reduce the rate of bleeding by tamponading the uterus, and buy time until suitable surgical control can be obtained.

- Abdominal aortic aneurysm: The MAST can be used to support a leaking aneurysm until surgery is commenced.

The MAST cannot be used to control arterial bleeding.

Provided the pressure in the MAST is maintained between 40 mm and 50 mm Hg, application for up to 72 hours does not have any reported complications.

However, prolonged use (greater than 90 min at full inflation pressure - 104 mm Hg)

can lead to compartment syndrome, acidosis, peroneal nerve injury, or skin necrosis.

Intravenous Lines

In principle, the shorter the line, and the wider the bore of the tubing and cannula, the faster the flow of fluid through that line.

Flow Rates (mL/min)

Cannula size	Crystalloid	Colloid
8.5 FG	1000 mL	600 mL
14G	125	90
16G	85	65
18G	60	35
20G	40	17

For the same gauge long line, flow rates are reduced as follows:

30 cm line	rate reduced by a third
70 cm line	rate reduced by a half

Infusion using a pressure infusion device will increase the flow rate by a factor of three.

Route of Administration

A minimum of a peripheral line and a central line is required. These lines should be independent of any lines used in the monitoring of the patient's circulation (CVP line), and should preferably be placed on the side of the patient remote from injury. Additional lines can be placed either centrally, or using the femoral route. The subclavian vein and/or the femoral vein can be accessed in 95% of cases, even when severe shock or cardiac arrest is present.

Central Lines

The usual site is either the subclavian vein or the internal jugular vein. In blunt polytrauma, where the status of injury to the neck has not yet been determined, the jugular should not be used because this will entail removal of the cervical collar, and possible moving of the neck. Consequently, the subclavian route is preferable in this situation.

Technique

The patient is placed supine, with the foot of the bed elevated. The head should be neutral, and it is not necessary to move the shoulders. Local anaesthetic should be usede where necessary. A 10 cc syringe, containing 5 mL of saline should be attached to the cannula, since a small piece of tissue is often "cored" into the cannula, blocking it. The syringe acts as a stabilising handle, and once under the skin, prior to entering the vein, a

small amount of saline can be injected, clearing the cannula. Entry is made at right angles to the midpoint of the clavicle, and two finger breadths below it. The needle tip is directed upwards towards the midpoint of the clavicle until it lies behind the clavicle, and is then directed medially towards the suprasternal notch. If light suction is applied to the syringe during advancement, a rapid flashback of blood will indicate entry into the vein.

Femoral Vein

The femoral vein forms a rapidly accessible (and underused) route of access to the circulation. Short-term (less than 48 hours) cannulation of the femoral vein does not lead to any increased risk of thromboembolism. Femoral vein puncture is possible, even with cardiac arrest due to ischaemia or hypovolaemia.

Technique

Use of the femoral artery allows the vein to be localised with ease. The vein, lying immediately medial to the artery can be accessed percutaneously. If the artery is not palpable then it lies at the junction of the medial and middle thirds of the inguinal ligament. Access to the femoral vein can be obtained 1.5 cm medial to this point.

Saphenous Vein

A direct cutdown on to the saphenous vein at the saphenofemoral junction can be used. The tubing from the administration set can then be placed directly into the vein.

Technique

Intravenous tubing is cut obliquely to form a bevelled edge. The leg is abducted slightly, and an incision made below and parallel to the inguinal ligament, extending from over the femoral artery, medially for a distance of 5 cm. The skin only is incised, and thereafter, blunt dissection is used to identify the saphenous vein, lying superficial and medial to the femoral vein. A segment of the vein is cleared, and elevated. A longitudinal incision is made in the anterior aspect of the vein and the tubing passed proximally up the vein for a distance of about 20 cm. Ties are placed distally and proximally around the vein and tubing. The skin is closed over the line.

Ischaemic Cardiac Arrest

Closed cardiac massage is ineffective following cardiac arrest due to hypovolaemia. Massage in general is only capable of achieving an output of 25% or less of the normal, and carotid blood flow is 10-17% of normal.

Open cardiac massage, following left lateral thoracotomy, raises the cardiac output to 35-54% of prearrest values, and the carotid output to 50%. These values may be raised even further if there is cross-clamping of the descending aorta so that until the circulation is filled, selective perfusion of the brain, and coronary circulation can be achieved.

In ischaemic arrest, therefore, open cardiac massage, after cross-clamping of the aorta,

with massive infusion of volume replacement offers the best chance of success. Metabolic acidosis should be corrected early with sodium bicarbonate, and the use of adrenalin may initiate a coarse fibrillation, which may then be corrected with a defibrillator.

Drug Therapy in Ischaemic Cardiac Arrest

The same drugs as in any other situation must be employed, bearing in mind that it is essential to remove the initial underlying cause (hypovolaemia). The following may be used for support:

- Dopamine

- Dobutamine

- Isoprenaline.

Dopamine

Dopamine is an immediate metabolic precursor of adrenalin and noradrenalin. It exerts a positive inotropic effect on the myocardium, acting on the B1 receptors. Dopamine also causes the release of noradrenalin from nerve terminals, thus acting without undue tachycardia. It increases systolic blood pressure with minimal effect on diastolic blood pressure. In relatively low doses there appears to be a specific renal effect, mediated by specific dopaminergic receptors. This results in an increase in the glomerular filtration rate, renal blood flow, and sodium excretion.

All traumatised patients with multiple-system involvement, especially if artificial ventilation or sustained hypotension is present, should be considered for a low-dose dopamine infusion, in a dose of 3-5 micrograms per kilogram body weight per minute.

Dobutamine

Dobutamine is a synthetic catecholamine which is more cardiospecific than either noradrenalin, or isoprenaline. It displays selectivity for the B1 cardiac receptors, and its primary action is to promote cardiac contractility. It acts directly, and does not cause noradrenalin release. Cardiac output is increased primarily by causing an increase in stroke volume. Consequently, dobutamine is of greatest value when the vascular compartment is full, and contractility is poor, such as myocardial contusion or exhaustion.

Normal doses are 3-10 micrograms per kilogram body weight per minute.

Isoprenaline

Isoprenaline is a synthetic sympathomimetic, related to adrenalin, which stimulates beta receptors directly, and produces an inotropic and chronotropic effect. For AV block with syncope or severe bradycardia, isoprenaline can be used to assist before pacing.

Normal dose is 10-60 micrograms by slow intravenous injection, followed by an

intravenous infusion of 5 micrograms per minute if required.

Myocardial Contusion

Myocardial contusion simulates the arrhythmic changes of myocardial infarction. Treatment is based on the presenting problem, and care should be taken not to further overload an already weakened heart.

Chapter 3.6: Current Concepts in Sepsis and Septic Shock

J. P. Pretorius

Introduction

Despite the development of increasingly powerful antibiotics, improved methods for haemodynamic monitoring and growing understanding of the underlying pathophysiology, septic shock remains a major clinical problem with unacceptably high morbidity and mortality.

Sepsis can be described as a spectrum of clinical states, or, the natural progression from colonization to infection to bacteraemia, sepsis, septic shock and multiple systems organ failure (fig. 3.6.1).

The clinical manifestations of sepsis in the very young, the elderly and the chronically debilitated, may be subtle, and can vary according to the stage of sepsis or the phase of septic shock.

From recent studies it has become clear that the septic response is a host-related phenomenon independent of the type of invading organism and its toxins. Microorganisms and their toxins may exert a direct damaging effect on human cells, but more important is the secondary systemic release of a wide variety of endocrine-like biochemical mediators that stimulate nonspecific local and systemic host defence mechanisms and also initiate immunologic, metabolic and neuroendocrine preparation for specific immune responses. Identical clinical manifestations can be seen in a diverse variety of organisms, but it has also been demonstrated that patients may develop the clinical picture of advanced sepsis in the absence of organisms. This is prognostically important because nonbacteraemic spesis carries a higher mortality rate. To summarize, sepsis causes a major derangement in all the organs and systems of the body that take part in the normal stress response. The result is a progressive impairment of the oxidative metabolism of circulating metabolic fuels, which are increased as part of the normal stress response. Slowly, a state of autocannibalization develops which progresses toa chronic shock state, termed *multiple systems organ failure,* and subsequently death.

Traditionally shock syndromes have been analyzed and treated according to their etiologies, such as haemorrhagic, cardiogenic, traumatic and septic shock. According to Shoemaker this approach, although simple, clear, logical, understandable and generally accepted, is an oversimplification, because most often clinical problems are complex with multiple etiologic factors. To be maximally effective, therapy of acute circulatory shock must

address all components of the disturbed circulation irrespective of the initiating event.

Multiple systems organ failure bears testimony to the inadequacy of approaching septic shock as a perfusion abnormality, since many such patients still die, albeit later, of multiple organ dysfunction despite initial resuscitation of circulatory abnormalities.

All states of shock can be viewed as multisystem syndrome. However, septic shock may be unique in that the fundamental defect in sepsis and septic shock may not be an inadequate supply of oxygen and nutrients to meet metabolic demands, but the inability of the body to use metabolic substrate effectively. This occurs before the manifestation of associated haemodynamic changes, hypovolaemia or cardiogenic shock.

Thepathogenetic mechanisms involved in septic shock are still unsolved and rational therapeutic regimens are still elusive.

Definitions

Any discussion of sepsis, septicaemia and septic shock requires clarification of terminology. To explain each disease state fully, it is perhaps best to consider various approaches to each, as no one definition can cover all aspects.

Shock

Acute, severe circulatory failure, regardless of etiology, has been termed shock. Circulatory failure occurs when transport of blood through the systemic circulation is not sufficient to provide oxygen and nutrients to vital organs or to remove accumulating metabolites at rates commensurate with metabolic requirements.

Cardiac function may be normal, at least initially, in many forms of circulatory failure, such as those that occur when the vascular volume is inadequate or when vascular tone is impaired.

The common denominator of shock, regardless of its etiology, is reduction of blood flow to vital organs due to reduction of total cardiac output or maldistribution of flow or both. The heart and peripheral vascular system are in dynamic equilibrium during the basal state, but this state of affairs is disturbed in many ways during shock. It is important to realise that the heart has relatively little effect on the normal regulation of cardiac output. Under normal conditions each organ has its own specific mechanism for regulating its blood flow - this is called autoregulation of blood flow, and cardiac output is a sum of all the flows through all the organs, In critically ill man, there seems to be a failure of microvascular autoregulation, so that O_2 uptake becomes more inherently dependent upon O_2 delivery than is normally the case (table 3.6.1). A prime function of the circulatory adjustment to surgical stress is the maintenance of an adequate O_2 delivery (DO_2) to subserve the metabolic demands of the cell machinery, both in the central and peripheral circulations. The stress of trauma or sepsis typically induces an augmented requirement for increased DO_2 because of increased cellular metabolic demand, as manifested by a measurably increased total consumption of oxygen by the body (VO_2).

The strength of ventricular contraction during shock states has generally been shown to decrease. Whether this represents altered ventricular loading or rate or reduced contractility, continues to be the subject of intense debate. It is important to distinguish between shock-induced alterations in cardiac dynamic function and shock-induced alterations in peripheral vascular function.

Irreversible Shock

Circulatory shock progresses through various phases, each characterized by specific clinical signs. If untreated, the final phase with any of the following elements, namely hypovolaemia, inadequate tissue perfusion, impaired oxygen utilization, exhausted metabolic energy reserves, myocardial decompensation and severe metabolic acidosis will develop into an irreversible cycle leading to cardiovascular collapse, multiple systems organ failure and death.

Thanks to concerted worldwide research efforts in all aspects of shock and resuscitation, clinicians today are able to treat the initial phases effectively by timeous, appropriate and prompt replacement of blood, fluids, and electrolytes, administration of inotropic and vasoactive drugs and in selected cases even by mechanical support devices such as intra-aortic balloon counterpulsation. Although circulation can now be restored in most patients, one must realise that all out therapeutic efforts amount to "buying time".

The final outcome depends on various factors such as the degree of anoxic cellular damage sustained during the period of shock, increased permeability of cell membranes and the capillary bed, the translocation of bacteria and absorption of endotoxin from the gut into the circulation. The pathogenesis of these events is not clearly understood at present, but they determine the development of sequential organ failure, often accompanied by systemic sepsis, seen in critically ill patients who have apparently been resuscitated successfully. It is this secondary chronic shock state with its accompanying multiple systems organ failure that now constitutes what used to be called irreversible shock (fig. 3.6.2).

Bacteraemia

"Bacteraemia indicates the presence of potentially pathogenic bacteria in the blood without signs of infection." Ledingham et al.

"Bacteraemia is not synonymous with septicaemia." Zimmerman

Bacteraemia is a transient phenomenon usually due to release of gram-negative bacteria in the bloodstream, as might occur, for example, after instrumentation of an infected urinary tract. The reticuloendothelial system usually manages to clear the bacteria from the circulation but, if not, septicaemia develops. Bacteraemia is characterized by sudden onset of rigors, confusion, hypotension, tachycardia and tachypnoea.

Septicaemia

"Septicaemia can be defined only imprecisely as a clinical state in which the patient is seriously ill from infection. Bacteria can generally be isolated from the bloodstream, but

many of the serious systemic effects are related to the production of bacterial toxins". Hanson

"Septicaemia is a clinical condition with a diversity of haemodynamic and metabolic features due to the presence of bacteria, their products, or other factors in the blood or tissues". Sibbald

"Septicaemia is a clinical syndrome commonly caused by gram-negative or gram-positive bacteria, comprising several of the following features: fever, hyperdynamic or hypodynamic circulatory shock, oliguria, thrombocytopaenia, lactacidosis, pulmonary oedema and intravascular coagulation." Ledingham et al.

"The physiologic response to septicaemia is a hyperdynamic state with a hypodynamic cardiogenic response being the result of superimposed myocardial depression occuring as a metabolic consequence of prolonged or severe sepsis." Wiles et al.

Septicaemia is the serious consequence of actively multiplying bacteria and their toxins in the bloodstream.

Endotoxaemia

"Endotoxaemia refers to the presence of a particular fraction of the wall of gram-negative bacteria in the blood". Sibbald

"Endotoxinaemia describes the presence of measurable amounts of endotoxin (lipopolysaccharide) in the systemic circulation". Ledingham et al.

Septic Shock

"When circulatory shock occurs as a complication of *severe infection* the condition is often described as septic shock". Rackow and Weil

"Shock may develop in infections due to bacteria, viruses, fungi, rickettsiae or protozoa. Septic shock is a *dramatic clinical syndrome* in which vasomotor collapse is associated with the presence of micro-organisms or their vasoactive mediators in the bloodstream". Karakusis

"Septic shock is a multi-system disease in which a complex set of host and invading organism interactions occur. It represents the natural progression of sepsis, with findings of hypotension and end-organ dysfunction secondary to impaired tissue perfusion or oxygen utilization". Ellrodt

"Septic shock is a *progressive state* of poor cellular and tissue perfusion leading to severe metabolic derangement, organ failure and multisystem deterioration associated with or induced by the presence of infectious agents in the bloodstream". Jacoby

"Septic shock describes a condition of cardiovascular collapse, principally or exclusively due to septicaemia. Hence it is the *end result* of an infective process originating in one or multiple foci which, apparently by means of endotoxin entering the systemic

circulation, affects all organ systems of the body". Ledingham et al.

"The manifestations of septic shock do not relate to a perfusion deficit but to the inability of the body to use existing metabolic substrate effectively". Mizock

Sepsis

"Sepsis is the clinical term for the systemic response to dividing and invading microorganisms of all types". Ayres

"Sepsis is an acquired disease process of intermediary metabolism induced by infectious agents. The nature and magnitude of this metabolic disorder produce a charateristic pattern of fuel-energy deficits and physiologic host responses that are not confined to any particular infectious agent". Siegel

"Sepsis denotes infection due to a variety of microorganisms or their toxins, associated with fever and toxic reactions". Ledingham

"Sepsis is defined as the physiologic alterations and clinical consequences of the presence of microorganisms or their products in the bloodstream or tissues". Harris

From the above-mentioned definitions it must be clear that septic shock is not synonymous with hypotension. It is difficult to differentiate septic shock from sepsis without shock because each appears to be a different stage in the spectrum of sepsis (fig. 3.6.1). Sepsis is the systemic, neurohumoral, metabolic and immune response to microbes. From its initiation this spectrum of infection-related responses is an extremely complex phenomenon with devastating consequences if neglected.

Classification and Stages of Sepsis and Septic Shock to Predict Outcome in Septic Surgical Patients

Etiologic Classification of Shock

It is convenient to classify shock according to the primary cause (table 3.6.2). Even such a simple classification emphasizes the diversity of etiologies leading to shock. More important is the fact that within a single category of shock, the dominant physiological derangements change as a function of time and therapy.

Table 3.6.2. Etiological Classification of Shock

Cardiogenic shock

Arrhythmias
- Bradyarrhythmias
- Tachyarrhythmias

Cardiac mechanical factors

Regurgitant lesions

Acute mitral or aortic regurgitation.
Rupture of interventricular septum.
Massive left ventricular aneurysm.

Obstructive lesions

Left ventricular outflow tract obstruction, i.e. congenital or acquired valvular aortic stenosis.

Left ventricular inflow tract obstruction, i.e. mitral stenosis.

Myopathic conditions

Impairment of left ventricular contractility, as in acute myocardial infarction.
Impairment of right ventricular contractility due to right ventricular infarction.
Impairment of left ventricular relaxation or compliance as in cardiomyopathies.

Obstructive shock

Pericardial tamponade
Coarctation of aorta
Pulmonary embolism
Primary pulmonary hypertension

Hypovolaemic shock

Haemorrhage
Fluid depletion or sequestration due to vomiting, diarrhoea, burnwounds, dehydration, etc.
Trauma

Distributive shock

Septic

Endotoxin
Live microorganisms
Specific infections, i.e. thyphoid fever or the toxic shock syndrome

Metabolic or toxic

Renal failure
Hepatic failure
Severe acid-base disturbances
Drug overdose
Heavy metal intoxication
Malignant hyperthermia

Endocrinologic

Diabetic ketoacidosis or hyperosmolar coma
Adreno-cortical failure
Hypothyroidism
Hyper- or hypoparathyroidism

Diabetes insipidus
Hypoglycaemia secondary to excess exogenous insulin or a beta-cell tumor

Microcirculatory impairment
Polycythaemia vera
Hyperviscosity syndrome, i.e. multiple myeloma
Sickle cell anaemia
Fat emboli

Neurogenic
Cerebral
Spinal
Dysautonomic

Anaphylactic

The traditional approach is therefore too simple in reality. The appropriate approach to evaluation of shock is to describe the temporal pattern of circulatory changes in the various clinical situations and to identify the underlying circulatory mechanisms and their mediators. This is essential to develop a rational and effective therapeutic regimen.

Classification of Shock According to Cardiopulmonary Function

In surgical practice the most common shock syndromes are haemorrhagic, traumatic, septic and cardiogenic shock (table 3.6.2). According to Shoemaker, oxygen delivery (DO_2) reflects circulatory function, while oxygen consumption (VO_2) reflects body metabolism. In shock the sequential patterns of DO_2 and VO_2 provide sensitive and specific criteria for evaluation of circulatory performance and metabolic function.

To illustrate the circulatory dynamics of shock states, Shoemaker considers pressure, volume, flow and function (VO_2) as the fundamental dimensions characterizing fluid systems.

In sepsis mean arterial pressure, volume and VO_2 decrease especially in the presence of dehydration, fever, diaphoresis and other extrarenal fluid losses. Marked increases in flow reflect compensatory increases in circulatory functions and increased VO_2 reflects increased metabolic demands as well as the prior oxygen debt. In the decompensated and terminal states, all variables decrease.

There are also several other clinical or functional classifications of the spectrum of sepsis. Traditionally the progression of haemodynamic changes observed during sepsis have simply been divided into high and low, or hyperdynamic and hypodynamic cardiac output states or warm shock and cold shock syndromes. Warm shock being defined as *increased cardiac output, vasodilation, increased systolic arterial pressure, pyrexia and a bounding pulse.* Cold shock is defined as *low cardiac output, intensive vasoconstriction, decreased mean arterial pressure, cold and clammy skin and a thready pulse.*

These syndromes are now known to represent unstable states in a clinical continuum of deteriorating haemodynamics. At best one can think of the cardiopulmonary manifestations

of sepsis in the temporal sequence of preshock, early shock and late shock states (table 3.6.3).

The concept that sepsis is an acquired disease of intermediary metabolism, induced by infectious agents, explains the intimate correlation between physiological and metabolic abnormalities in severe human sepsis, and suggests that the fundamental mechanisms of physiological compensation are directly mediated by the categoric necessity of responding to the abnormal metabolic process.

Siegel attempted to define the haemodynamics of sepsis and also to determine whether the variables monitored would enable discrimination between septic and non-septic states. After sufficient volume resuscitation it was noted that stress responses fell into four major groups.

In physiologic terms, the A state is the normal stress response seen in compensated sepsis and after trauma or major surgery. A sympathetic response characteristically increases the heart rate and cardiac index as well as myocardial contractility. Compared to the normal or reference state, this hyperdynamic state displays increased oxygen consumption but the sympathetic adaptive response occurs without evidence of metabolic abnormality and minimal respiratory dysfunction. It is abnormal to be unable to achieve this A state response in the presence of major stress.

The B state is also a hyperdynamic cardiovascular state, but it represents increasing severity or progressive deterioration or decompensation in the septic process. This state displays a decrease in vascular tone (lowered SVR) that is disproportionate to the increase in cardiac output. The compensating sympathetic responses are therefore unable to supply peripheral needs.

Consequently, oxygen consumption is reduced because of decreased oxygen extraction, seen as a narrow arteriovenous oxygen content difference. A metabolic acidosis now develops. This B state reduction of VO_2 is a direct manifestation of reduced cellular oxidative metabolism.

In the C state respiratory decompensation (retention of CO_2 with profound respiratory acidosis) is superimposed on the unbalanced septic process and metabolic acidosis of the B state. It is characteristic of profound septic shock with hypotension despite normal or increased cardiac output.

The D state represents primary myocardial failure rather than peripheral failure. It includes low cardiac output, high SVR, wide SVR, wide arteriovenous oxygen content difference and reduced VO_2. Because of insufficient peripheral flow, extraction of oxygen increases. This D state therefore is a delivery failure rather than an extraction failure as in the B state. Patients usually present in the D state if they have preexisting myocardial disease. It can also occur as a result of biventricular septic myocardial depression in which it may be a manifestation of myocardial metabolic insufficiency in association with or after a period of profound B state hyperdynamic metabolic insufficiency.

The cardiovascular reaction to the septic process is best understood as an adaptive response to the underlying metabolic abnormalities reflected in the physiologic state.

Clinical Stages of Multiple Systems Organ Failure

Appreciation of the physiological-biochemical interaction helps to make the septic multiple systems organ failure syndrome (MSOF) understandable. The strong association between uncontrolled infection and the subsequent evolution of multiple systems organ failure has been aptly described by Fry: "Bacterial invasion continues to be the inciting event that tips over the first piece in what one can truly view as a biologic domino effect. Unless some form of effective intervention is achieved, MSOF will result in the demise of these patients". As an element of the spectrum of sepsis (fig. 3.6.1), it must be realised that MSOF syndrome *per se* has an insidious onset and can progress through various clinical stages (table 3.6.4).

Evaluation of surgical intensive care unit mortality revealed that septic general surgical patients did not die acutely. Instead, regardless of shock or infection, salvageable candidates survived their acute insult. When the primary process is slow to respond or refractory to treatment, organ dysfunction increases progressively. According to Jordan, when multiple organ dysfunction is viewed as a consequence of sepsis, its progression or resolution indicates the patient's severity of illness.

Scoring Systems to Assess Patients with Surgical Sepsis

Correction of deranged physiology is one of the main aims of intensive care. Continued interest in diagnosis and treatment of surgical sepsis requires an accurate unitary standard by which the severity of illness due to, the efficacy of treatment on, and the prognosis of the physiological derangements of sepsis may be measured. The difficulty in appreciating the extent and complexity of the insult induced by sepsis and the level of adequacy of the host defense mechanisms is related to the lack of precise measurement of the specific cellular biochemical lesions involved.

In recent years several investigators have developed various methods to assess the clinical status of severely septic surgical patients.

With these methods it is possible to:

- quantify the severity of sepsis

- monitor the course of sepsis sequentially

- match septic patients populations

- predict the clinical outcome of sepsis.

Scoring systems that yield objective descriptions of the patient's condition at specific points in the disease process, aid our understanding of the complex nature of surgical infections, as well as the multifaceted aspects that must be considered when treating and supporting patients with surgical sepsis.

Future investigations of patients with serious infections should incorporate one of the published severity of illness scores as part of the description of the patient population. Such

information would make meticulous monitoring of organ function easier in susceptible patients, and also help to identify dysfunction at an earlier stage, thus allowing timeous prophylaxis or therapeutic interventions. This may reduce the incidence of sequential organ failure and death.

Surgeons treating critically ill septic patients, are often confronted by questions such as:

- Is reoperation or further surgical drainage or debridement required for recovery in a specific patient.

- When is it necessary to transfer a specific septic patient to the intensive care unit?

- Are the chosen antibiotic and the dosage level administered effectife for this particular patient?

- How can new therapeutic regimens be evaluated in a spectrum of septic patients already receiving complex multidisciplinary treatment?

Clearly, the answer no longer lies in our nonquantitative general clinical impression of the patient's condition alone. Today the clinical acumen of the astute surgeon can be strengthened by objective scientific measurements obtained by employing one of the various scoring systems available. These systems are not intended to be prescriptive or absolute and it is well to remember not to become complacent about a patient with a score within the range of safety or to be fatalistic in dealing with a patient with a score above the cut-off point of safety. This new science can never eliminate all of the uncertainty inherent in medical management, but it does show promise of improving out comprehension of the relationship between intensive medical treatment and patient outcome.

Before attempting to use a particular scoring system it is necessary to familiarize oneself with the intentions of the authors thereof. Strict adherence to their instructions will ensure success. Most systems are only variables which are commonly available in most hospitals. Uniform criteria for diagnosis of infection (i.e. table 3.6.5) and multiple organ failure are also essential (i.e. table 3.6.6).

Some authors employed a pure acute physiology score (APS) which is a physiologic index to measure the severity of illness; others used indexes specially designed for conditions of sepsis. Stevens devised a scoring system to represent the magnitude and severity of organ failure. He defined seven organ systems and assigned a score from 0 to 5 in each system (table 3.6.7).

Scores were calculated by squaring the value assigned to each system because the degree of risk seems to rise exponentially with the number of organ failing. The three highest scores were added to arrive at the **"septic severity score".** The theoretical range of scores under this system is 0-75. Evaluation of this system showed that for patients with a score of > 40 the mortality rate was 21% and 32% in two subsequent studies. The overall accuracy for both studies was 77%. Another approach to grading the severity of sepsis which gave similar results when tested, was published by Elebute and Stoner in 1983.

In 1982 Knaus et al recognizing the need to describe accurately and to classify groups of patients on the basis of severity of illness, proposed the APACHE or *acute physiology and chronic health evaluation score* as a system for this purpose. The original APACHE called for 34 laboratory or physiological variables as well as a chronic health evaluation. There was significant redundancy in the requested data and subsequently Knaus and his associated published the APACHE II system. This uses only 12 initial values of routine physiologic measurements - all must be obtained to have a valid score. The APACHE II score is composed of three parts (table 3.6.8):

- the acute physiology score composed of the 12 laboratory and physical variables

- points for age baove 44 years

- points for chronic health problems.

The range of potential scores is 0-71. Scores above 30 are associated with a mortality rate of at least 70% and scores above 40 are uncommon. This refined system has been tested extensively by Knaus and associates as well as others.

Knaus et al also developed objective physiologic criteria for the diagnosis of organ system failure (OSF)(table 3.6.6) with the aim to provide estimates of the probability of survival for intensive care patients. In a large study, outcome at discharge from hospital was investigated.

It was found that:

- A single OSF lasting for more than 1 day resulted in a mortality approaching 40%.

- TwoOSFs for more than 1 day increased the mortality to 60%.

- Three or more OSFs persisting for more than 3 days further increased the mortality 98%.

They concluded that prognostic information, when properly used, could improve both the quality and compassion of their care. In general, risk factors influencing the development of organ failure or death can be divided into:

- Patient factors which include:

    - The type of disease

    - Physiological reserve

    - Severity of disease

    - Response to therapy

- Treatment factors which include:

- Type of therapy available

- Use or application of therapy.

Pine et al identified clinical shock, malnutritionl, alcoholism and age as important predictive factors.

Epidemiology

The epidemiology of fulminant infection and septic shock in critically ill surgical patients, is the study of the spatial, temporal and population distribution, as well as the specific etiology of, and the contributing factors in the pathogenesis of this disease.

Sepsis is an acquired disease of intermediary metabolism induced by infectious agents. The nature and magnitude of this metabolic disorder produce a characteristic pattern of fuel-energy deficits and physiologic host responses that are not confined to any particular infectious agent.

The natural progression of unchecked serious infection, with findings of hypotension and end-organ dysfunction secondary to impaired tissue perfusion or oxygen utilization is termed *septic shock.*

It is difficult to estimate the magnitude of the septic shock problem because these syndromes are not reportable and review of death certificates probably underestimates the problem, because septic shock may not be reported in patiens with severe underlying diseases.

Bacteraemia can be classified as primary and secondary, where the former denotes those cases in which no source could be identified or the source is traced to contaminated intravascular devices or fluids. Secondary bacteraemia are those infections in which the source of infection was secondary to an identifiable distal septic process. An anatomic area is considered to be the source when its bacteriology is identical to the blood bacteriology. Most nosocomial sporadic bacteraemia are secondary, and most epidemic bacteraemias are primary.

Incidence

The overall incidence of gram-negative sepsis has continued to increase during the past two decades and remains high today despite more and better antibiotics and other advances in medical and surgical practice. Its prevalence is higher in large university medical centres than in community hospitals due to difference in the patient populations treated, as well as the invasive diagnostic and therapeutic procedures undertaken. According to a survey done by the Centre for Disease Control (CDC) in 54 hospitals in the USA, the incidence of primary bacteraemia per 1000 discharged patients was:

Non-academic hospitals: 1.3
Small academic hospitals: 1.7
Large academic hospitals: 3.8
Mean: 2.

They also found that primary bacteraemia forms the following percentage of all nosocomial infections:

Non-academic hospitals: 5.8
Small academic hospitals: 4.8
Large academic hospitals: 6.6
Mean: 5.9.

It has been shown that the specific incidence of bacteraemia and fungaemia varies according to specialty service. The highest was 14.5 episodes per 1000 admissions occuring on a medical service followed in descending order by surgical (9.3/1000), obstetric (5.3/1000) and gynaecologic (4.6/1000) services. Although septic shock may be seen in patients with viral, fungal or parasitic infection, it is seen most commonly in bacterial infections - especially gram-negative bacteria. It must be remembered that various other states of shock may occur in association with infections through specific mechanisms related to the type and location of the infection but are *not* included in the septic shock "syndrome" and will not be discussed in this chapter. Examples are hypovolaemic shock from infectious diarrhoea and exotoxin-associated vascular collapse as in the toxic shock syndrome.

The Centre for Disease Control reviewed much of the reported data on the incidence and mortality from gram-negative rod bacteraemia and concluded that the incidence in the USA was probably between 100000 and 300000 cases per year.

Fatality Rate

The case fatality rate of septicaemia is determined by the total number of deaths due to septicaemia, divided by the total number of patients diagnosed as septicaemic, expressed as a percentage. The fatality rate is subjected to wide institutional variation for the same reason as the incidence of septicaemia, namely university and large municipal hospitals generally care for patients with more complicated or later stages of disease. Many series have reported that mortality of gram-negative septicaemia has ranged between 20% and 50% with a definite increase in those with adverse host factors such as neutropaenia and immunosuppression.

Shock complicates gram-negative sepsis in approximately 40% of cases. When infection progresses to septic shock, fatality rates of up to 47% have been found. On the other hand patients who do not develop shock will have a fatality rate of only 7% to 10%.

For gram-positive bacteraemia with and without septic shock, the fatality rates are 33% and 8% respectively.

Weinstein et al found in their analysis of 500 episodes of bacteraemia, a total fatality rate of 42%. About half of all deaths were directly attributable to infection. The fatality rate also varied according to specialty service: it was 2.6% among obstetrical-gynaecological patients, 42% among medical patients, 49% among surgical patients, and 60% among transplant patients.

Distribution

Place of Acquisition

Most gram-negative bacterial infections, except those of the urinary tract, are more prevalent in hospitalized patients. It is also rare for septic shock to present as a community acquired disease. It seems that the proportion of septicaemic cases that are community acquired, depends to a large extent upon the population of patients at the institution involved. Weinstein et al reported in their study that two-thirds of all the septicaemic episodes were community acquired at a community hospital, half were community acquired at a city hospital, and only about one third were community acquired at their academic hospitals. The fatality rate of nosocomial septicaemia is increased substantially. It has been reported to be 50%-300% higher than the fatality rate from community-acquired infection.

The trend toward increased incidence nosocomial bloodstream infections, particularly those due to gram-negative bacteria, reflects primarily more vigorous, invasive care for conditions that would have been rapidly fatal previously, i.e. severe burns, multiple organ trauma, malignant diseases, immune compromised patients and multiple systems organ failure.

Population Susceptibility

During recent years the age of the hospital population has shifted toward a greater proportion of elderly patients. Consequently chronic diseases, malignancy and impaired defence mechanisms are common and predispose these patients to infections. This is extremely important, because the nature and severity of the host's underlying disease is the major determinant of outcome of septicaemia. McGowan et al have shown that the incidence of septicaemia is high among the elderly and among children less than 10 years of age.

Determinants

The inherent biological characteristics of micro-organisms, as well as current hospital practices, are partially responsible for the increased incidence of these hospital-acquired infections in patients with more severe underlying diseases and altered host defence mechanisms.

The determinants of infection can therefore be described as:

- Specific, i.e. the microorganisms involved

- Contributory, i.e. the risk factors predisposing the individual to infection.

Microbiology of Septicaemia and Septic Shock

Bloodstream infections usually represent the most serious extensions of a process that initially involves local sites such as the skin, urinary tract, respiratory tract and mucous membranes of the gastrointestinal tract (table 3.6.9).

The identification of the etiologic agent has important therapeutic implications in

patients with infection and septic shock because it may be caused by both gram-positive and gram-negative bacteria, as well as fungi, viruses and parasites. In fact, any polysaccharide or protein foreign to the circulation is likely to cause an inflammatory reaction and stimulate the immune mechanisms. In addition most organisms have specific toxins with discrete actions of their own. The exact mechanism of this trigger-host interaction remains unsolved. Nevertheless, it appears to be host dependent rather than organism dependent.

Gram-positive bacteria are morphologically distinct from gram-negatives. Gram-positive organisms are surrounded by a thick multilayered coat of peptidoglycan which is associated with teichoic acid. This permeable coat acts as a highly selective cation exchanger. Gram-negative organisms are more highly evolved and their single layer of peptidoglycan is surrounded by an impermeable layer of lipopolysaccharide.

At the end of the previous decade approximately 70% of all hospital-acquired infections for which cultures were obtained, were caused by aerobic gram-negative bacilli. During recent years it has been observed that gram-positive cocci may be emerging as important pathogens - especially methicillin sensitive and resistant Staphylococcus aureus, Staphylococcus epidermidis and the enterococcus. The most frequently isolated gram-negative bacilli were E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Enterobacter spp (fig. 3.6.3). It is noteworthy that the P. aeruginosa has been consistently associated with the highest mortality of all septicaemic infections (fig. 3.6.3).

In all likelihood this is a manifestation of its association with neutropaenia and diseases such as leukemia and extensive burns, which have the more adverse prognosis. Similarly, gram-negative organisms cause septic shock in more than two-thirds of all cases of gram-negative septicaemia. The upsurge of the incidence of gram-negative septicaemia is a development that has followed the introduction of antimicrobial agents about forty years ago, as well as other parallel advances in medical and surgical practice. Today, the syndrome of gram-negative rod septicaemia constitutes one of the major if not the principal infectious disease problems encountered in modern medical centres.

Despite this, Staphylococcus aureus remains a most important hospital pathogen and the commonset cause of infection following clean surgery and procedures such as the insertion of intravascular devices. It is as common as E. coli. Whilst S. aureus if frequently a primary pathogen and thus capable of causing serious infection in previously healthy people, the coagulase negative S. epidermidis (especially slime producing strains) is a secondary pathogen or opportunist, rarely able to cause infection without the aid of prostheses or intravascular devices. These coagulase-negative staphylococci were long regarded only as laboratory contaminants, which of course they still sometimes are. During the 1980s, however, they have become increasingly important nosocomial pathogens, particularly in oncology, neonatology and intensive care.

Fungi are also being recognized with an increased frequency as important pathogens in surgical patients. The problem is that clinical studies do not provide complete information because the size of the population at risk is usually not described and, since fungal infections often remain undiagnosed, the true frequency is difficult to define. Until more reliable diagnostic tests become available, many fungal infections will only be suspected by clinicians. Candida species have been the most frequently cultured fungal organisms, with C. albicans

and C. tropicalis as the most virulent. Candida spp are common colonizers which can be cultured from 10%-50% of oropharyngeal and gastrointestinal specimens in the normal host. In immuocompromized patients chronic serious fungal infections such as aspergillus fungus balls in the lung, and candida hepatitis are also being diagnosed more often. Moreover, new fungal pathogens are still being identified. Two important clinical variables are responsible for the apparent increasing incidence:

- Broad spectrum antibiotics are used widely and may result in suppression of normal bacterial flora with opportunistic Candida overgrowth being the consequence.

- The enormous advances in support technology during the last decade has permitted the critically ill to survive for longer periods of time, becoming particular candidates for opportunistic pathogens like Candida spp. It is suggested that candidaemia may represent failure in host defense and not infection in the traditional sense, in most patients.

Candida is a common contaminant of central venous catheters (15%-70%). Antibiotic therapy, total parenteral nutrition and major stress such as extensive burn wounds, extensive surgery and organ transplants, lead to increased rates of colonization. Alterations in host defense may lead to invasion and infection. Fungal overgrowth within the gastrointestinal tract by Candida has been generally accepted as an important feature of systemic candidiasis. The gastrointestinal tract then becomes a reservoir for contamination of other areas, or may actually result in direct penetration of the organism into the mesenteric lymphatic channels or portal venous circulation. Dyess et al found a synchronous septicaemia with candidaemia in 34% of cases. Patients with polymicrobial infections had poorer survival rates. Hepatic failure is also known to be associated with candidaemia. Defective hepatic reticuloendothelial function may permit systemic dissemination.

The Environment

The proportions of organisms that were community acquired (CA) and hospital acquired (HA) during a study by Weinstein et al showed that E. coli, the organism most commonly isolated, was community acquired in 42% of cases in contrast to other members of the family Enterobacteriaceae, which were much less commonly acquired outside hospitals. Pseudomonas and other nonfermentative facultative gram-negative bacilli with more resistant antibiotic susceptibility patterns, were mostly hospital acquired. As a group, gram-negative organisms accounted for the majority of bacteraemic isolates. The fact that fungaemias (especially Candida) were responsible for 8% of all isolates, may be a consequence of the increasing sophistication and invasiveness of modern medicine. Most S. aureus isolates were hospital acquired, while Pneumococci were community acquired 80% of the time. Anaerobes which have been identified in up to 10% of bacteraemias in other series, constituted 13% of isolates in this series.

Differences Among Various Disciplines

There are striking differences in the frequency with which particular organisms cause septicaemia on the different hospital services. S. aureus accounted for a significant proportion of isolates on medical (18%) and surgical (11%) services but was rarely found to cause septicaemia elsewhere. Enterobacteriaceae accounted for 25%-37% of isolates on all services

except obstetrics.

Sources of Septicaemia

It is generally agreed that the key factor in treating sepsis is identification of the source, location and type of offending organism. As this is often not easy to accomplish, knowledge of the epidemiology of septicaemia as well as surveillance of local patterns of septicaemia may aid in the diagnosis and selection of rational empiric therapy for serious infections in critically ill patients. The respiratory and genitourinary tracts are often cited as the most common sources of septicaemia, with the gastrointestinal tract in the third place.

S. aureus septicaemia is most often secondary to respiratory tract infection. Skin infections and especially intravascular catheters were also common foci. The sources of septicaemia involving gram-negative facultative bacteria reflect the organ systems and parts of the body in which these organisms are found ordinarily. Therefore E. coli septicaemia is most often found secondary to genitourinary tract infection and is also associated with abscesses, biliary tract infections and respiratory tract infections. Anaerobic septicaemia generally follows genitourinary and bowel sepsis while Candida fungaemia tends to be respiratory and genitourinary in origin. Nevertheless, each episode of septicaemia must be viewed in its own right and be interpreted with circumspection.

Virulence and Invasiveness of Bacteria

Microbial pathogenesis focusses mainly on two areas (table 3.6.10):

- The antigenicity of cell-wall structures which give the organism some advantage against human host defence mechanisms.

- Bacterial products such as enzymes, toxins or metabolic by-products which may cause tissue damage.

Table 3.6.10. Bacterial Features Probably Responsible for "Virulence" of Pathogenic Gram-Negative Bacteria

1. Capability to adhere to mucosal surfaces.

2. Serum resistance, i.e. not lysed by complement-mediated serum reactions.

3. Capsular surfaces enabling resistance to phagocytosis.

4. Bacterial cell walls with an antigenic composition similar to host tissue, i.e. blood group determinants.

5. Toxic cell wall constituents, capable of eliciting inflammatory and pyrogenic reactions.

6. Ability to survive intracellularly and thus evading host defense mechanisms.

7. Direct toxicity of bacterial enzymes and toxins affecting host tissue and initiating infection as well as lethal sequelae.

Although bacteria are clearly involved in sepsis and septic shock, interpretation of the extent of their role in the pathogenesis of the sepsis continuum has changed in recent years. It is now generally accepted that host defense and environmental factors exert a major influence on the development of septic shock in conjunction with the release of endotoxin. Endotoxins are lipopolysaccharide (LPS) constituents of the gram-negative bacterial cells wall (fig. 3.6.4). The latter consists of three layers which constitute various antigens. The outer membrane contains protein, lipid and carbohydrate arranged in polysaccharides. Most distal to the cell wall is the "O"-polysaccharide domain of LPS, consisting of linear or branched polysaccharides. These outer chains are highly species variable and represent the bacterial "O"-antigenic determinants which in the past have been referred to as synonymous with endotoxin. We know today that most, if not all, of the biologic activities of LPS appear to be lipid associated. The O-antigenic grous are not directly important in toxicity but, in part, responsible for the microbial properties of resistance to phagocytosis in effect permitting the microbe to evade engulfment unless specific antibodies are present. Linking this "O"-polysaccharide to the inner lipid of LPS is the R-core region composed of a ketodeoxyoctanoate sugar backbone (KDO). Innermost and acting as a hydrophobic cell wall anchor for LPS is lipid A. This concealed position of lipid A partly explains the lack of normal antibodies to this antigen. Lipid A consists of D-glucosamine disaccharide units which are attached to KDO. In turn lauric, myristic, palmitic and beta-hydroxymyristic acids are attached to the disaccharide. Betahydroxymyristic acid is unique to lipid A and is believed to be the toxic moiety of the molecule - they insert into cell and mitochondrial membranes and also bind calcium and magnesium ions. The biochemical structures of lipid A from different gram-negative bacilli are similar. It is lipid A that is detected by the Limulus assay for endotoxin.

Endotoxin is normally bound to the outer surface of gram-negative bacteria but is released into solution when bacterial cells undergo lysis. It is an extremely potent toxin causing clinical symptoms at plasma concentrations as low as 1.10^{-9} g/mL. Endotoxin is very stable chemically and is not inactivated by boiling. The endotoxin may thus be fully potent, although the bacteria which produced it are dead already.

The intermediate or murein layer of gram-negative bacterial cell walls is rigid material composed predominantly of peptidoglycan or mucopeptide. It is primarily at this stie that agents that inhibit cell-wall synthesis, such as penicillins and cephalosporins, have effect, resulting in osmotically unstable microbial forms. In that instance the structure responsible for retention of the integrity of the microbe is the inner or cytoplasmic membrane.

Many gram-negative bacteria also have one or more flagellar structures or "H"-antigen which confer properties of motility - examples are P. aeruginosa and E. coli. Many of these organisms contain structures called pili or fimbriae lying outside the outer membrane. These protein structures seem to be important for attachment or adherence of bacteria to mucosal surfaces. Organisms such as E. coli or Klebsiella spp. in addition have a capsule, the "K"-antigen, lying exterior to the "O" antigen. One of the more confusing aspects of the bacterial cell wall composition is the structural interrelationship of the components described above, the assessment of their pathological role, and the interaction of these factors with host defense

mechanisms. Although the bacterial cell wall has been represented schematically in fig. 3.6.4 three-dimensional structural analysis reveals that there is no definite demarcation between one structure and another.

Bacterial Resistance

The evolution of bacterial enzyme systems began long before the existence of man, some probably to protect them from toxic substances produced by fungi or other bacteria. Now, as medical science develops a therapeutic advantage, the evolutionary process continues and bacteria develop modifications that make them more resistant to antibacterial therapy. Overall, the development of resistance is unavoidable. Increasing numbers of resistant gram-negative bacilli usually appear within a few years after the introduction of new antimicrobials.

The major factors contributing to the development of bacterial resistance is selective pressure, which increases markedly with prolonged therapy, whether empiric or prophylactic, and sustained use of inappropriate or only marginally effective antibiotic agents. This occurs primarily within the hospital rather than in the community and it partially reflects the intensity of antibiotic use. The greatest impact of a selective process is seen in some hospitals, where the repeated exposure of bacteria to antibiotics has led to the development of "pools" of highly resistant pathogens (table 3.6.11). Fortunately several investigators have presented evidence that control of antibiotic usage will result in reversion of the bacterial population to sensitive organisms.

Tanle 3.6.11. "Pools" of Resistance Within Hospitals

Burn units
Intensive care units
Respiratory equipment
Hospital personnel
Patients with chronis illness

Micro-organisms have evolved an array of ingenious alterations that allow them to survive in the presence of antibiotics. This may originate through the development of mutations or by selection of increasingly more resistant strains of bacteria. Mutations may occur at random events without exposure to the drug in question. An example is the penicillinase-producing S. aureus, which is said to be naturally resistant. Selection is the process that occurs when micro-organisms, which have acquired resistance to a particular antibiotic, multiply unimpaired. Sensitive strains are suppressed and in time the resistant strains predominate. Analysis indicated that these strains have undergone a stable genetic change that may persist in the absence of the drug.

While mutation is frequently the cause, resistance to antimicrobial agents may also be acquired through transfer of genetic material from one bacterium to another by transduction, transformation or conjugation. Transduction occurs when a bacteriophage (a virus that infects bacteria) carrying bacterial DNA within its protein coat, infects a bacterial cell. If this genetic material includes a gene for drug resistance the bacterial cell may become resistant to the agent and capable of passing this train on to its progeny. This process is particularly important among strains of S. aureus where some phages can carry plasmids (extrachromosomal genetic

material) that code for penicillinase or betalactamase, while other tranfer information for resistance to erythromycin, tetracycline or chloramphenicol. When DNA that is free in the environment, is incorporated into bacteria, the process is called transformation. The importance of this method is unknown. Conjugation is an extremely important mechanism for the spreading of antibiotic resistance - especially as far as multiple drug resistance is involved. In this progress genes are passed from cell to cell by direct contact through a sex pilus. The transferable genetic material consist of two different DNA sequences. The first sequence codes for the actual resistance and is termed the resistance (R) factor, or the R determinant plasmid. For example, in the case of aminoglycodise resistance, the R factor codes for the synthesis of drug-inactivating enzymes. The second sequence codes for a sex factor, which is the transfer apparatus and is termed the resistance transfer factor (RTF). These sequences can be transferred individually, but both must be present for successful transfer of resistance to antibiotics. Conjugation is the predominant mechanism of transfer of genetic information among gram-negative bacteria. Conjugation can take place in the gut between nonpathogenic and pathogenic bacteria. The proportion of enteric bacteria that carry plasmids for multiple drug resistance has risen slowly in the past 25 years. Antibiotics can exert a powerful selective pressure to allow emergence of such resistance strains.

The mechanisms of resistance are likely to involve permeability changes, target site changes, or enzyme production, i.e. beta-lactamases. One or more mechanisms may be present in a given resistant organism (table 3.6.12). A specific problem related to beta-lactamases is the fact that, in contrast to the more widely-known consitutive enzymes which are produced at a relative constant rate, some beta-lactamases are inducible. Non-fastidious, gram-negative bacilli such as Enterobacter species, Citrobacter freundii, species of Serratia, indole-positive Proteus, Providentia, Pseudomonas and Acinetobacter, possess the ability to rapidly develop resistance to many of the new "enzyme-stable" beta-lactam antibiotics. The immune compromised host, exposed to pools of resistance within hospitals (table 3.6.11), will inevitably be at risk of infection, specifically from some of these organisms. This poses many clinical problems. As resistance emerges during therapy, therapeutic alterations are severely limited - especially because multiple resistance may arise simultaneously. Outbreaks of nosocomial infections with these multiple drug-resistant organisms and spread of the strains throughout the hospital are already being seen. The use of new antibiotics should be judicious and restricted.

In summary, gram-positive bacteria produce a large amount of beta-lactamase that is secreted extracellularly. The information for staphylococcal penicillinase is encoded in a plasmid, and may be transferred by phage to other bacteria; the enzyme is inducible by antibiotic substrates. In gram-negative bacteria, aerobic and anaerobic, beta-lactamases are found in small amounts located in the periplasmic space of the cell wall. Since the enzymes of cell wall synthesis are located on the outer surface of the inner membrane (fig. 3.6.4), these enzymes are strategically located for maximal protection of the microbe. Beta-lactamases of gram-negative bacteria are encoded either on chromosomes or plasmids, and they may be constitutive or inducible.

Risk Factors Predisposing the Individual to Infection

Host factors and therapeutic interventions predispose the patient to bacteraemia and determine outcome. Since the patients who are most susceptible to opportunistic infection tend

to have more frequent and invasive interventions, it is often difficult to distinguish the relative contributions of host and infectious hazards.

Most such infections occur in patients with impaired defence mechanisms or when bacilli are introduced directly into a site susceptible to infection, such as the urinary, respiratory or vascular system, by a urinary or intravenous catheter or ventilatory equipment. Perhaps the most decisive factor is the severity of the host's underlying condition. Granulocytopaenia specifically appears to be the single most important factor leading to the development of gram-negative bacillary infections and modifying its severity (table 3.6.13).

Table 3.6.13. Risk Factors

Host Related Factors

I Development of Bacteraemia

1. Granulocytopaenia

Total PMN < 500 cells/mm^3: considerable risk
500-1000 cells: moderate risk
> 1000 cells: normal risk

2. Severity of underlying disease
3. Extremes of age
4. Diabetes mellitus
5. Multiple organ failure (heart, liver, kidney, lung)
6. Massive burn injury
7. Multiple serious injuries

II Development of Septic Shock

1. Age < 10 or > 50
2. Hypothermic: inability to mount a fever > 37.5 °C during first 24 hours
3. Debilitation
4. Chronic ill health:
   - hepatic dysfunction
   - cardiac disease
   - congestive heart failure
   - renal disease
   - diabetes mellitus
   - alcoholism
   - azotaemia
   - malnutrition

III Factors Influencing Outcome of Bacteraemia

1. Underlying disease

    Cirrhosis/Alcoholism
    Haematologic malignancy
    Other neoplasms
    Renal failure
    Diabetes mellitus
    Severe burns/Trauma
    Neutropaenia
    Hypogammaglobulinaemia

2. Clinical shock

    Duration of hypotension
    Anuria
    $VO_2 < 170$ mL/min/m^2
    $DO_2 < 600$ mL/min/m^2

3. Grade of severity of bacteraemia or fungaemia

    polymicrobial bacteraemia

4. Age

5. Multiple organ failure: respiratory, renal, hepatic, cardiovascular

6. Significant lactate accumulation

7. Failure to develop fever at the onset of sepsis

Treatment Related Factors

I Development of Bacteraemia

1. Imunosuppression

    Adrenocorticosteroids
    Irradiation
    Cytotoxic drugs

2. Intravascular devices

    Central venous lines, especially with total parenteral nutritition
    Intra-arterial catheters
    Swan-Ganz catheters
    A-V shunts for haemodialysis

3. Urethral catheters

4. Endotracheal tubes and ventilatory equipment

5. Prior administration of antimicrobial drugs

6. Hospitalization for surgery

II Development of Septic Shock

1. Immunosuppression as above

2. Previous antibiotic therapy

3. Various invasive devices

4. Failure to drain a purulent collection

III Factors Influencing Outcome of Bacteraemia

1. Immunosuppression

2. Inappropriate or previous antibiotic therapy

3. Delayed admission to an intensive care unit

4. Diminished cardiac output, which fails to improve with therapy

5. Surgery in the presence of corticosteroid therapy

6. Persistant peripheral vasodilation

7. Certain combinations:

    Corticosteroids, surgery, diabetes
    Malignancy and corticosteroids
    Surgery and renal failure.

Catheter-related septicaemia or fungaemia is the most frequent life-threatening complication of central venous devices and occurs with 3% to 7% of catheters. Most of these septicaemias begin with either contamination of the hub of the catheter, or with local infection of the catheter punction site. The majority of catheter-related infections derive from infection of the transcutaneous tract which become colonized with organisms from the patient's own cutaneous flora during insertion of the catheter or thereafter. Cooper et al found organisms most often on the outer surface of infected catheters rather than in the lumens. Although coagulase negative staphylococci, i.e. S. epidermidis, account for the largest proportion of colonized catheters, gram-negative bacilli or Candida species most often cause catheter-related septicaemia.

In a recent study by Yeung et al it was found that all types of central venous catheter could be used with safety for up to four days, but that the risk of infection increased rapidly thereafter. Similar to other studies, they reported approximately a threefold greater risk of infection for triple lumen versus single lumen catheters, regardless of the usage of the catheter. Patients receiving total parenteral nutrition through a triple lumen catheter were at greatest risk of infection (14.5%). The multiple ports allowing multiple infusions through separate channels in a single catheter, increase the amount of manipulation of the system and apparently increase the chance of infection. A strict basic catheter-care protocol must be followed and all possible precautions must be taken when using these catheters. When administering total parenteral nutrition, a single lumen catheter should be used and reserved for this purpose only.

The use of an indwelling bladder catheter for more than three days is associated with at least an 80% incidence of urinary-tract infection and a 10% incidence of bacteraemia. Colonized respiratory equipment such as ventilators, humidifiers and nebulizers can cause outbreaks of infection due to bacteria such as Pseudomonas or Serratia, by direct aerosolization of organism into the lungs. Contamination of equipment such as endoscopes, pacemakers, dialysis machines etc can also cause infections. Similarly, parenteral and enteral feeding solutions contaminated during preparation can give rise to serious infection. Factors that predispose the bacteraemic patient to develop septicaemia or septic shock are less clearly defined than those associated with the development of bacteraemia. Seriously ill, hospitalized patients, especially those in intensive care units, constitute a preselected population which are most at risk to develop septic shock (table 3.6.13).

Pathophysiology

The pathogenetic mechanisms of sepsis and septic shock are much more complex than in other shock states. Understanding the sequence of events, the cellular consequences and humoral chain reactions that take place during the development of the spectrum of sepsis is essential for achievement of optimal regimens for shock management. Unfortunately, the pathophysiology of sepsis and septic shock, particularly the dynamic interaction of the various humoral cascade systems of the systemic immune response, which are activated directly by bacteria or their products, is not yet fully understood. Major reasons are firstly, the problem of trying to relate cause and effect in studies of the critically ill human considering the multifactorial influences of underlying disease, acute serious bacterial infection and all the therapeutic modalities involved. Many of the changes observed either clinically, or in laboratory investigations, may not be the manifestations of the infection itself but of a primary disease that is complicated by an infection. Secondly, there is a major problem in translating the results of studies in different animal species to the human clinical setting. Despite these limitations, several pathophysiological observations have been made in human sepsis in regard to sequential haemodynamic changes and potential mediators. Simplistically, one can regard sepsis and septic shock as an interaction between an organism and/or toxins acting as a trigger, and a host.

It is very important to emphasize again that the pathogenetic focus has moved in recent years from the role of the bacteria to the role of the host. Increasing attention is bein paid to elucidate the complex disturbances of host defence. The human being possesses many defence mechanisms, which may be activated variably depending on the trigger, host factors

and underlying disease process (fig. 3.6.2). Unfortunately, it is often difficult to delineate primary pathogenetic mechanisms (trigger-host) from secondary reflex responses (host-host) and responses due to disordered end-organs such as the heart and lungs. Thomas very aptly said: "It's our response to their presence (bacteria) that makes the disease. Our arsenals for fighting off bacteria are so powerful, and involve so many different defence mechanisms, that we are in more danger from them than from the invaders. We live in the midst of expolosive devices; we are mined. When we sense lipopolysaccharide, we are likely to turn on every defence at out disposal: we will bomb, defoliate, blockade, seal off, and destroy all tissue in the area. Leukocytes become more actively phagocytic, release lysosomal enzymes, turn sticky, and aggregate together in dense masses, occluding capillaries and shutting off the blood supply."

If bacteraemia is transient, the result may only be a mild febrile reaction with little if any haemodynamic or neuro-endocrine response. In a more severe situation where bacteraemia progresses to septicaemia, the body's physiological compensating mechanisms, activated by the host defence system, are able to support the patient, provided that the primary septic focus or infection can be eradicated. On the other hand, protracted activation of the systemic immune response by persistent sepsis in a susceptible host or in the presence of predisposing factors, will cause the clinical manifestations observed in severe bacterial infections. Septic shock arises as a hyperacute incident when the compensating haemodynamic mechanisms are unable to maintain adequate tissue perfusion in the presence of persistent peripheral vasodilation.

Host Defence Mechanisms

Host defence mechanisms are essential for the survival of mankind. Currently, realization of the limitations of antibiotic therapy emphasizes the need for a new dimension in the treatment of sepsis. Understanding the role of the immune and inflammatory antibacterial host defence mechanisms may lead to the ability to modulate these mechanisms to help control sepsis. Host defence systems are organised into local and systemic mechanisms (table 3.6.14), but form a very effective integrated ensemble to protect the host against infection.

Table 3.6.14. Host Defence Mechanisms

Local Defences

Normal indigenous flora
Morphologic integrity of body surfaces
Normal excretory secretions and flow

Systemic Defences

Non-Specific Inflammatory System

Acute phase reactants
Phagocytosis
Natural antibodies
Hormonal factors
Nutrition

Specific Immune Systems

Humoral immunity: plasma, cells and antibodies
Complement system
Granulocytic phagocytosis
Cell-mediated immunity
Lymphocytes and lymphokines
Macrophages and monokines.

Local Defences

Because of their general nature, the non-specific local mechanisms are difficult to quantify, and because they are so efficient, they are often taken for granted. Viewed together, the effect of this first line of defense is impressive; taken individually, each component is of much smaller magnitude and less dramatic than are specific immune responses.

Under normal circumstances humans have an abundant native microbial flora (table 3.6.15).

Table 3.6.15. Bacteria That Most Commonly Colonize Healthy Human Body Surfaces (Normal Flora)

Skin:

Staphylococcus epidermidis
Corynebacterium sp.
Propionibacterium acnes
Staphylococcus aureus
Streptococcus pyogenes
Gram-negative bacilli

Nose:

Staphylococcus epidermidis
Staphylococcus aureus
Streptococcus sp.

Mouth and Oropharynx:

Streptococcus sp.
Anaerobic gram-negative sp.
Veilonella sp.
Fusobacterium sp.
Bacteriodaceae sp.
Staphylococcus epidermidis
Lactobacillus sp.
Neisseria sp.
Haemophilus sp.
Anaerobic streptococci and micrococci
Peptococcus
Peptostreptococcus
Actinomycetes
Staphylococcus aureus
Gram-negative bacilli

Esophagus and Stomach:

Low numbers of surviving bacteria from upper respiratory tract and food.

Small Intestine:

Lactobacillus sp.
Gram-negative anaerobic sp.
Bacteroides sp.
Clostridium sp.
Enterococcus
Enterobacteriaceae

Large Intestine: (95% or more species are obligate anaerobes)

Gram-negative anaerobes
Bacteriodaceae sp.
Fusobacterium sp.
Gram-positive anaerobes
Peptococcus sp.
Peptostreptococcus sp.
Clostridium sp.
Enterobacteriaceae
E. coli
Klebsiella sp.
Proteus sp.
Enterococcus
Lactobacillus sp.
Streptococcus sp.
Staphylococcus sp.

Pseudomonas sp.
Acinetobacter sp.
Alcaligenes sp.

External Genitalia and Anterior Urethrae

"Skin flora"
Gram-negative anaerobe sp.
Enterococcus
Fusobacterium sp.

This includes both gram-positive and gram-negative organisms which form an important host-parasite relationship with man. This relationship may be symbiotic, commensal or parasitic. The normal commensal flora play an important role in protecting the host from microbial invasion by pathogenic organisms. This is possible through mechanisms such as:

- Competition for the same nutrients.

- Competition for the same receptors on host cells.

- Production of bacterial products that are toxic to other organisms.

- Stimulation of cross-protective immune factors or natural antibodies.

The dynamic interaction between the native flora and potential pathogens normally protects the host against colonization. These organisms that make up the normal flora are influenced by many environmental factors such as diet, personal hygiene, and sanitation. We are exposed daily to many potentially pathogenic aerobic bacteria which may be present in food and drink, but man, with the help of his intact defence mechanisms, is able to cope with the daily concentrated supply of bacteria.

The morphologic integrity of the skin and mucous membranes is another important and effective first line of defense. The relative dryness, the desiccating effect, the mild acidity, the desquamation of skin and the normal skin flora act in concert to form an effective prohibitive environment. Although the mucous membranes are exposed to a larger number of microorganisms, they present a mechanical barrier. The surfaces are bathed in secretions with antimicrobial properties due to the presence of enzymes such as lysozyme, specific immunoglobulin namely IgG and secretory IgA, and iron-binding proteins. It has recently been recognized that iron is important for bacteria, and that body fluids exposed to microbes contain iron-binding proteins as another protective mechanism.

In the respiratory tract, expulsion of the particles by coughing and sneezing, combined with the humidification ofinspired air, and the trapping effects of hairs and mucus in the nasal passage, as well as the mucociliary mechanism of the tracheobronchial tree, are remarkably efficient defence mechanisms. On the alveolar level macrophages and tissue histiocytexs play a more prominent role. In the gastrointestinal tract the acid pH of the stomach and the various enzymes in bile and pancreatic secretions are important antibacterial factors. In the bowel, competition of the normal flora plays an important protective role. The washing effect of tears

and urine also assist in the repulsion of invading microorganisms.

Nevertheless, local defences are not infallible. Infections generally begin when microorganisms which are already colonizing the patient, breach the patient's local defence mechanisms. Practically all infections in the compromised host are caused by more or less fourteen aerobic organisms which are potential pathogens. They can be divided into two groups:

Community-Acquired Bacteria

Streptococcus pneumoniae
Haemophilus influenzae
Branhamela catarrhalis
Escherichia coli
Staphylococcus aureus
Candida albicans (fungus)

Hospital-Associated Bacteria

Klebsiella
Proteus
Morganella
Enterobacter
Citrobacter
Serratia
Acinetobacter spp.
Pseudomonadaceae

Varying percentages of people carry the community-acquired microorganisms in the throat or gastrointestinal tract, but it is uncommon for healthy people to carry hospital-associated microorganisms. These eight microorganisms only colonize people with impaired host defences, such as hospitalized patients with underlying disease. Failure of local mechanical defences may range from the loss of skin in the burn patient, to the loss of gastrointestinal integrity in a patient with a leaking anastomosis or perforated viscus. Further, following major surgery or trauma the defence mechanisms are often altered, resulting in a decreased resistance to colonization, to which is added the risk of the invasive devices necessary for treatment. In spite of infection-control policies, nosocomial infections with bacteria colonizing various body surfaces remain common.

Although the focus of infection can be identified in most patients, there is an increasing number of cases with "septicaemia" in whom a source of infection is never found. From laboratory, as well as clinical studies employing surveillance techniques, there is good evidence that the gastrointestinal tract often serves as the primary reservoir for bacteria causing life threatening infections. This phenomenon in which viable bacteria or endotoxin contained in the gut, can cross the epithelial mucosal barrier to cause infection, is called translocation. Translocation is promoted by disturbance of the ecology of the normal gastrointestinal flora, resulting in bacterial overgrowth. Impaired host defenses as well as physical disruption of the mucosal barrier also allow translocation. After thermal injury, a

rapidly fatal septic syndrome can develop, originating from indigenous bacteria normally colonizing the gut. The relevance for surgical patients is the fact that translocation will occur even in healthy individuals with normal bowel flora, provided the stress is large enough.

Systemic Defences

From the preceding discussion it is clear that the ultimate defence against microbial pathogens is provided by the specific immune defence mechanisms (table 3.6.14).

Nonspecific Inflammatory System

According to Deitch, the nonspecific inflammatory immune system is the primary defence ofthe nonimmune host, since it does not require a previous exposure to the invading microorganism to be activated and therefore can respond immediately to protect against the invading bacteria. This system represents the tissue-injury recognition phase or the local inflammatory response which is initiated when bacteria invade tissue. The cellular elements involved initially include mast cells, tissue macrophages, monocytes and systemically recruited neutrophils. The humoral components include plasma proteins such as fibronectin and components of the coagulation and complement cascades, plus humoral antibodies and the vasoactive amines (fig. 3.6.5).

Figure 3.6.5. Cellular and Humoral Interactive Response Due to Infection

The biologic effects of gram-negative bacillary endotoxins (lipopolysaccharides) are complex and interrelated. Both in vitro and in vivo endotoxins have at least four pathophysiology effects: they can activate the complement, coagulation, and fibrinolytic systems and can trigger a series of enzymatic reactions leading to the release of bradykinins and possibly other vasoactive peptides that can cause hypotension.

The humoral components of this nonspecific immune system modify the local environment to limit the spread to invading bacteria, and they render the bacteria more susceptible to phagocytosis through the process of opsonization. It also recruits phagocytic cells of which the neutrophil is the most important.

Specific Immune System

The specific immune system consists of two distinct functional components (table 3.6.14), namely the cell-mediated immune system (CMI) and the antibody-complement-phagocyte immune system (ACP).

The Cell-Mediated Immune System

The CMI system consists of macrophages anmd lymphocytes and their non-antibody products called monokines and lymphokines (collectively cytokines), which are important mediators in the pathogenesis of shock and chronic disease states. Functions of the CMI include:

- Activation of macrophages to become more effective phagocytes.

- Activation of killer lymphocytes that are directly cytotoxic for target cells coated with antibodies.

- The production of natural killer lymphocytes which can kill cells in the absence of antibodies.

The exact mechanisms controlling cell-mediated immunity are unclear. It appears that both macrophages and lymphocytes are comprised of multiple subpopulations of cells that have either inhibitory or helper functions. Cytokines serve as the primary messengers that transmit information between the various cell populations, to reduce or enhance the immune response (fig. 3.6.6).

Figure 3.6.6. Immune Cellular Interactions During Sepsis

Lymphokines and monokines serve as the primary messengers that transmit information between the various cell populations.

A simplified outline of some of the major relationships between the various mononuclear subpopulations. Solid lines indicate pathways that increase the immune response while the broken lines designate pathways that down-regulate the immune response. Humoral factors (monokines and lymphokines) serve as the primary messengers that transmit information between the various cell populations. Two of the best described humoral messengers are interleukin-1 (IL-1), produced by facilitory macrophages and interleukin-2 (IL-2) produced by helper T-cells.

According to Abraham, cell-mediated immunity is primarily a function of thymus-derived or T lymphocytes, which represent more or less 70% of the peripheral blood lymphocytes. T cells can kill intracellular microorganisms, tumour cells and cause rejection of allografts, but are inadequate to protect the host from rapidly proliferating extracellular bacteria and their toxins. Nature has solved this by providing the humoral or antibody-mediated immune system.

The Antibody-Complement-Phagocyte System

In contrast to the phylogenetically more primitive nonspecific inflammatory system, the ACP system responds specifically to antigenic sites on the surfaces of invading bacteria to which the host has previously been sensitized. The system specifically eliminates most species of bacteria and some viruses. It is based primarily on B cell function. The B cells represent approximately 15% of the normal peripheral blood lymphocytes. Bacterial antigens induce humoral immunity when they are presented by macrophages to helper T cells which then liberate lymphokines, i.e. interleukin-1, that instruct B cells to differentiate into antibody-producing plasma cells (fig. 3.6.6). Of the five main classes of antibodies IgA and IgG are the most important. IgG is the most abundant and consists of four subclasses, IgG1-4. The major function of the IgG antibodies is protection of tissues against bacterial invasion.

IgA antibodies are differentiated specifically to protect vulnerable mucous membranes. The IgA-producing plasma cells colonize the underlying lymphoid tissue lining the mucous membranes. IgA antibodies do not activate complement or phagocytes. Their primary function

is to prevent adherence of microorganisms and viruses to mucosal surfaces. The IgA-coated microorganisms are then washed away by body secretions.

The major function of the antibody-complement-phagocyte system is to identify, opsonize or weaken and then to phagocytose invasive microorganisms. According to Anderson this is achieved during a process consisting of five stages:

- Bacterial recognition and binding by specific IgG antibodies.

- Activation of the entire complement system, in a cascading manner, to generate a large antimicrobial complex which can damage bacterial cell walls. Proinflammatory mediators (C3a, C3b, C3e, C5a) are also released during activation.

- C3a and C5a effect chemotaxis or leucotaxis. The efficiency of this process is time-dependent.

- Phagocytosis follows consisting of three substages: opsonization, immune-adherence and ingestion. IgG-antibodies and C3b are the important opsonins which neutralize the antiphagocytic capsules of pathogenic bacteria, so that the phagocytes (polymorphonuclear leucocytes) bind to the bacteria.

- Once ingested, the bacteria are destroyed by powerful intracellular antimicrobial systems.

Immunocompetence

Immunocompetence is a relative quality. What would be competent for one type or route of infection may be inadequate for another. Nevertheless, host defence homeostasis implies that local and systemic immune mechanisms (table 14) are intact and appropriately regulated. Van Saene has summarized the host defence mechanisms into two functional categories namely:

- Colonization defence: This is the mucous membrane and skin-associated preventive mechanisms based on neutralizing and not on killing aerobic microorganisms attempting to colonize the mucosae and skin. Infection defence: This second line of defence is situated behind the skin and mucous membranes and comprises the systemic defence mechanisms aimed at killing the aerobic invaders.

A patient may acquire microorganisms from the hospital environment and develop a carrier state. This will be followed by an endogenous infection only if and when the host suffers impairment of defence against both colonization and infection. Illness promotes many immuno-deficiencies, and in the critically ill, these deficiencies are amplified. According to Pinsky and Matuschak et al: "The normally integrated process of inflammation operates within a restricted environment to contain, suppress, and eliminate infecting organisms, and to clear damaged tissues of cell debris and foreign material. The host usually pays a price for this process: abscess formation with local tissue destruction. When the inflammatory process is not contained, a generalized activation of inflammatory effector cells, including neutrophils, macrophages and lymphocytes, ensues. Through such an uncontrolled 'malignant' intravascular

inflammatory response, the vascular endothelium is damaged and direct immunological cytotoxicity can further impair organ function. The important point is that this impairment of systemic host defences most probably leads to an early, generalized endothelial-cell injury that simultaneously affects multiple organs. The inflammatory process may become selfperpetuating and "malignant" because of:

- spill-over of bacteria and their byproducts into the circulation.

- inadequate regulation of the inflammatory response by the host.

- hepatocellular substrate oxidative failure.

Why regulatory control is lost in some cases, is not yet fully understood. The liver which contains most of the fixed macrophages of the body as Kupffer cells lining the extensive sinusoidal network of the liver, may play a pivotal role as a regulator of systemic host defences.

The principal mechanisms are the following according to Matuschak:

- Control of systemic endotoxaemia, bacteraemia and vasoactive byproducts of sepsis: The role of circulating gram-negative bacterial endotoxin in the pathogenesis of the sepsis syndrome has been investigated extensively. It may include:

- direct cytotoxic effects of endotoxin on endothelial cells.

- induction of endothelial cell surface factors that promote neutrophil adherence.

- activation of phagocytes.

- triggering of the complement cascade.

- triggering of the kinin system.

- triggering of the coagulation cascade.

- synergistical alteration of endothelial-cell metabolic function and structural integrity.

The major mechanisms whereby hepatic macrophages (reticuloendothelial system, RES) limit the magnitude and duration of systemic endotoxaemia are the uptake and detoxification of endotoxin. Normally, the in-series intestinal barrier and efficient Kupffer cell uptake of bacteria and their products in portal blood provide an effective first line of defence.

- Regulation of the generation of endogenous inflammatory mediators by mononuclear phagocytes: All macrophages, including the Kupffer cells, are target cells for endotoxin. The liver can therefore "export" a wide range of macrophage-derived endogenous mediators such as cachectin, interleukin-1, arachidonic acid metabolites and platelet-activating factor. These monikines mediate most acute pathophysiologic reactions formerly attributed to endotoxin. This includes fever, hypotension, neutrophilia, neutropaenia, thrombocytopaenia, disseminated

intravascular coagulation, inflammatory cell activation, as well as systemic immune and metabolic chnages.

- Metabolic inactivation of inflammatory mediators by hepatocytes: Changes in normal hepatocyte performance and hepatobiliary excretory function can significantly compromise host defence. Hepatocytes can clear endotoxin from the circulation under certain circumstances. They can also clear certain mediators.

- Synthesis of proteins essential in the host inflammatory response and intermediary metabolism: Interleukin-1 activates the hepatocytes to reprioritize protein synthesis to increase the release of acute phase proteins such as fibronectin, C-reactive protein, fibrinogen, ceruloplasmin and alpha1-antitrypsin, while albumin, transferrin and alpha1-macroglobulin are reduced. Acute phase reactants participate actively in many aspects of host defence.

The Role of Inflammatory Mediators

The results of recent work have demonstrated that many of the observed acute-phase responses are mediated by host-secreted cytokines, in particular, the secretory products of activated macrophages. According to various workers, one of these cytokines, cachectin or tumour necrosis factor (TNF), has emerged as a particularly important mediator of normal tissue homeostasis as well as inflammatory responses. It has direct effects on cellular function and indirect effects mediated by other peptide and lipid inflammatory molecules.

According to Sherry and Cerami, the capacity of TNF to mediate the inflammatory response; to modulate the metabolic activities of diverse tissues; and to augment the function of other cytokines requires that its synthesis and release be closely controlled in vivo. They also suggest that:

- local production of TNF at a site of injury might act to limit tissue damage and to promote wound healing and tissue remodelling. This has also been reported by Urbaschek.

- Moderate systemic levels of the hormone might confer a survival advantage with respect to bacterial or viral infection by providing a useful mobilization of energy reserves for the acute metabolic demands of inflammatory responses.

- In sharp contrast to these beneficial effects, prolonged exposure to even low levels of TNF might contribute to the cachexia associated with chronic disease states.

- Rapid uncontrolled production of TNF, like that observed in response to endotoxaemia or overwhelming gram-negative sepsis, could act systemically to induce the metabolic derangements of septic shock leading to cardiovascular collapse, acute organ failure and death.

Collectively, the systemic sequelae observed during the acute-phase response include (fig. 3.6.7):

- Fever, and a negative nitrogen balance.

- Mobilization of amino acids fro the peripheral tissues.

- An increase in synthesis of hepatic acute-phase proteins.

- Prominent leukocytosis with neutrophilia.

- Redistribution of plasma trace metals: levels of iron and zinc decrease while copper rises.

- Neuroendocrine changes, including a rise in circulating levels of insulin, glucagon, glucocorticoids, catecholamines, beta-endorphins and growth hormone.

- Increase in energy expenditure, which differs from exercise or starvation in that a greater proportion of amino acids especially branch amino acids, are used as a fuel substrate.

- Elevated intracellular calcium levels may represent a final common pathway to cell death, because of inhibition of mitochondrial oxidative phosphorylation.

Figure 3.6.7. Effects of IL-1 and TNF on host substrate metabolism

Cardiovascular Dysfunction

According to Parillo, septic shock is associated with serious abnormalities at two sites within the cardiovascular system. Almost all patients initially develop a severe decrease in systemic vascular resistance due to diffuse arteriolar vasodilation. This persistent, severe peripheral vasodilation may be due to circulating mediators such as the potent vasodilator adenosine which is produced during the degradation of ATP or inorganic phosphate that accumulates when insufficient ATP is generated. The mediators involved in septic shock can generally be divided into two groups:

1. Vasoconstrictors

Catecholamines
Angiotensin
Vasopressin
Serotonin
PG2Falpha
TXA2
MDF

2. Vasodilators

Histamine
Bradykinin
PGI2, PGE1
H+, K+
Beta-endorphins
Adenosine

False neurotransmiters.

Stimulation of the autonomic nervous system may also influence the tone of vascular beds. The term peripheral vascular failure has been coined to describe this phenomenon. This condition is usually associated with increasing blood lactate levels and carry a poor prognosis although cardiac output is often maintained.

The exact mechanism is not known, but marked loss of autoregulation within the microvasculature with subsequent mismatch between oxygen demand and supply, is probably a central mechanism leading to widespread and irreversible damage.

During early septic shock, arteriolar vasodilation accounts for most of the decreased vascular resistance. Later in the disease's evolution, the vessels of the microvascular bed are occluded by both neutrophil microemboli and severe vasoconstriction in some regions. Because bloodflow is shunted around these capillary beds through the nonoccluded, dilated arterioles, peripheral resistance is decreased even further (fig. 3.6.8). As the common denominator of nonsurvivors of septic shock seems to be persistent vasodilation, it can be assumed that these patients are more likely to die of peripheral vascular failure than of cardiac failure.

Figure 3.6.8. Pathogenesis of Cardiovascular Dysfunction in Sepsis

The later phase of septic shock is also associated with down-regulation of alpha-receptors, inability to maintain peripheral vascular tone, increased capillary permeability and leakage, increased venous capacitance and a decreased venous return.

Resuscitation of patients with septic shock generally requires massive volumes of fluid and many patients develop gross peripheral oedema during the evolution and treatment of septic shock. This is due to a reduced capacity in septic patients to retain fluids in the vascular system as well as an increase in microvascular permeability. Changes in the distribution of blood volume, the regional balance in microvascular pressures, membrane permeability and lymph flow determine the extent of protein and fluid transfer in septic shock, and thus, to what extent the intravascular and extravascular distribution of fluids and proteins is affected.

The increase in venous capacitance leads to sequestration of blood in peripheral vascular compartments, causing further deterioration of the circulation.

The second site of cardiovascular abnormality is the heart itself. It has been demonstrated in several septic shock animal models that myocardial performance *per se* is abnormal already during the early phases of the disease. Cardiac preload, hear rate or contractility may be impaired. Recently it has been shown that coronary perfusion is usually well-preserved in human septic shock. Therefore coronary hypoperfusion and myocardial ischaemia does not seem to play a role during septic shock and this hypothesis can no longer be used to explain the pathogenesis. Another proposed mechanism that may induce myocardial dysfunction is the presence of circulating myocardial depressant substances. There is ample evidence to prove the existence of such substances in clinical and experimental models. At present it is not certain whether there is only one or perhaps several degradation

products with negative inotropic properties which are released during serious sepsis (fig. 3.6.8).

Another recent finding has been that the LVEF is often depressed in septic shock. Some investigators have observed that such a decrease in LVEF is mainly found in survivors together with LV dilatation. Others failed to show this relationship. Inability to increase the LV diastolic size may be related to myocardial oedema and may carry a poor prognosis.

It has recently also been observed that in certain patients with pulmonary hypertension, RV dysfunction may predominate. In these cases RVEF decreases the RV dilation is observed. This makes the RV more vulnerable to decreases in coronary perfusion pressure.

Oxygen Delivery and Utilization in Sepsis

Proper cell function requires a continuous supply of energy to maintain cellular integrity and to allow for important activities such as protein synthesis, muscular contraction and active transport. According to Dantzker, energy is derived from food, predominantly through oxidative phosphorylation via the Krebs' cycle. Oxygen is the terminal electron acceptor in this cycle and sufficient amounts are required if optimal use of substrate for the generation of ATP is to continue. In anaerobic situations the more wasteful method of ATP generation, through glycolysis is relied on. As O_2 is the most indispensable of all cellular nutrients, the shock state may be viewed as a cellular disease: a state of acute cellular O_2 deficiency, whether it be from a limitation of flow or impaired circulatory function as reflected by DO_2 (DO_2 = arterial O_2 copntent x cardiac output), or a potential limitation of all oxidative metabolic reactions as reflected by VO_2 (VO_2 = arteriovenous oxygen content difference x cardiac output)(table 3.6.1). Coetzee defines an effective circulation as *bloodflow which will ensure an adequate DO_2 to meet the current VO_2*. The determinants of DO_2 are cardiac output, haemoglobin concentration and the oxygen saturation of arterial blood. Based on this, the maintenance of a high haematocrit seems essential for optimal DO_2 (table 3.6.1). Nevertheless, studies of the effects of increasing red cell concentrations on the viscosity of the blood have shown that the optimal haematocrit was about 32% in postoperative patients, although some organs appear better able to respond to both increases and decreases in the haematocrit. It has also been observed that the haematocrit in the microvasculature differs from that in arteries and veins. The microvascular haematocrit can change independently of the systemic haematocrit, depending on alterations in the microenvironment which enable the vascular bed to alter flow and cross-sectional area. Capillary DO_2 may therefore be difficult to predict.

The ability of oxygen to diffuse into the tissues is determined by the resistance to the diffucion of oxygen and the driving pressure gradient of capillary PO_2 to the mitochondria. The effect of tissue oedema or inflammation on the diffusing characteristics of the tissue are likely to play an important role.

If DO_2 is reduced experimentally, VO_2, a measure of the activity of the aerobic pathway, is maintained until a very low value, the critical DO_2, is reached (fig. 3.6.9). Initially, physiological compensation takes place as the percentage of oxygen extracted from the blood increases. This increases the oxygen extraction ratio (VO_2/DO_2). If the DO_2 falls below the critical value, the VO_2 will also fall despite the fact that the extraction ratio

continues to increase. VO_2 is therefore dependent of DO_2 above the critical DO_2 value, but supply dependent for values below the critical value. It seems reasonable to increase DO_2 to a supply-independent plateau in an effort to prevent multiple systems organ failure. Unfortunately, too little is known at the moment about oxygen metabolism at the cellular level to judge the correctness of this assumption.

Figure 3.6.9. DO_2/VO_2 Relationship

The possible pathological supply dependency of sepsis. Due to the abnormal pattern of oxygen utilization during sepsis the curve is shifted to the right and a supply dependency is also observed over a wider range of DO_2. The level at which the curve plateaus during sepsis has not been established for humans. A recent study has demonstrated an increase in the critical DO_2 during bacteraemia in dogs, but not a true supply dependency over the range encountered in patients.

During sepsis patients experience haemodynamic abnormalities. The hyperdynamic state of sepsis, which is often dependent on the adequacy of fluid resuscitation, increases DO_2. Patients who deteriorate due to their sepsis, show a fall in cardiac output which may curtail DO_2 markedly. The most important finding seems to be the fact that the compensatory increase in the oxygen extraction ratio is an insufficient response to the decreasing DO_2. According to Dantzker this supply dependency of VO_2, which is often associated with lactic acidosis, suggests that oxygen demands were not being met adequately even in the presence of an increased DO_2, during hyperdynamic sepsis. A possible explanation for the abnormalities of oxygen extraction and utilization is an inability of the microvasculature to provide sufficient oxygen to actively metabolizing the tissues. This could be the result of diminished autoregulatory control and capillary damage, which results in maldistribution of blood flow. Consequently the oxygen transport system becomes inefficient as large quantities of the conventional oxygen supply bypass certain parts of the microcirculation, to such an extent that pathological supply dependency of VO_2 develops. This may be an indication of a significant deficit in tissue oxygenation and an important facet of the pathogenesis of multiple systems organ failure.

Too much emphasis is placed on analysis of arterial and mixed venous blood and measurement of lactic acidosis, which when abnormal only indicate anaerobic respiration that has proceeded unabatedly, until the rate of lactate production has overwhelmed the compensatory hepatic, renal and skeletal muscle clearance mechanisms. It appears that tissue will functionfor as long as adequate ATP is available. For that reason, monitoring of the metabolic products of ATP metabolism, i.e. adenosine and hypoxanthine may be a useful index of cellular energy production. More accurate indicators of tissue oxygenation are needed. Direct assessment of cellular bioenergetics by spectro-fluorometry or magnetic resonance spectroscopy holds promise for the future.

Nevertheless, considering the present state of the art, clinicians should guard the adequacy of tissue oxygenation in septic patients carefully. Evidence that endotoxin and sepsis affect cellular respiration and oxidative metabolism is controversial. Changes in mitochondrial function appear to be more consistent with tissue hypoxia than disordered cellular functioning such as metabolic uncoupling. Shoemaker has demonstrated that maintaining DO_2, and thus VO_2 at higher than normal levels ($DO_2 > 600$ mL/min/m^2; $VO_2 > 167$ mL/min/m^2) by volume

loading and the infusion of dobutamine, improves the survival of critically ill postoperative patients. This ability to increase VO_2 by augmenting DO_2 provides evidence of the tissue's ability to utilize oxygen when it is available. An abnormal DO_2 rather than VO_2 seems to be the crux of the matter.

Clinical Manifestations of Sepsis

Sepsis may be present with manifestations ranging from subtle to fulminant. The diagnosis of sepsis in a patient with hyperpyrexia, rigors and hypotension is obvious. On the other hand, candidaemia is an example of a serious infection which may develop insidiously. The clinical symptoms and signs of sepsis are the result of activation of the endogenous, protective physiological processes described in previous sections. The patient may present at various stages of the clinical spectrum of sepsis, ranging from bacteraemia to septic shock and even organ failure (figure 3.6.10). Progression of the disease process is dependent on the continued presence of unresolved infection. Repeated, meticulous observations of the patient's vital signs ("trending") will provide valuable early clinical warning of impending septic shock.

Fever

Fever is the manifestation which most often raises suspicion of infection. Fever is induced by the release of bacterial pyrogenic substances, which stimulate monocytes and macrophages to produce endogenous pyrogenic reactions. TNF, interleukin-1 and interferon alfa, secreted by the mononuclear cells, express pyrogen activity by increasing prostaglandin E_2 synthesis in or near the hypothalamus. This resets the body's thermoregulation mechanism to a higher level.

The question of whether or not the febrile response is beneficial to the host, remain unanswered. Moderately elevated temperatures might enhance bactericidal activity. Many clinicians will treat hyperpyrexia (> 40 °C) because of the high physiological demands on the patient, and to give symptomatic relief to the patient. Although septic patients are usually pyrexial, normothermia and hypothermia may also be present. Failure to mount a febrile response may indicate a poor prognosis. This is usually found in very young or very old patients, chronic debilitation, alcoholism or uraemia. The principle of management of pyrexia is the treatment of the underlying infection.

Cardiopulmonary Manifestations

According to Harris, the best way to understand the cardiopulmonary manifestations of sepsis, is to look at the temporal sequence of preshock, early shock and late shock (table 3.6.3, figure 3.6.10).

In the preshock state, cardiac output increases to compensate for the decreased peripheral vascular resistance. Mean arterial pressure may be lower than normal, but not in the shock range. This hyperdynamic phase has well-perfused warm extremities due to vasodilation.

During early septic shock, systemic vascular resistance declines even further, leading to hypotension. This is mediated through stimulation of the kallikrein system. Cardiac output

is still increased due to adrenergic stimulation and vasodilation, but it can no longer maintain adequate perfusion pressure and shock ensues. The extremely low peripheral vascular resistance is very useful in the differential diagnosis, and usually implicates sepsis. A low peripheral vascular resistance and a high cardiac index is also useful to distinguish sepsis from other causes of hypothermia. The level of vascular resistance is not related to prognosis. The haemodynamic picture is more host dependent than organism specific. Septic shock does occur more often in gram-negative infections, but the haemodynamic manifestations are nonspecific and do not exclude other pathogens.

In the latter phases of shock, cardiac output is normal or diminished. The impairment of myocardial performance still seems to be potentially reversible. The role of a myocardial depressant factor remains controversial. During sepsis venous capacitance, ventricular compliance and performance change and this makes the interpretation of CVP and PCWP inaccurate. A rising CVP or PCWP may reflect the course of sepsis but it is difficult to distinguish between the effects of fluid therapy and progressive ventricular dysfunction. During late septic shock, there is usually no response to volume loading, and a PCWP of 14-15 mm Hg should be regarded as the cut-off point. Although it is generally accepted that lactic acidosis reflects anaerobic metabolism in poorly perfused tissue, there is very little evidence to support this. Inadequate hepatic and renal lactate clearance are probably just as important as increased tissue production. In late septic shock decreased cardiac output aggravates acidosis because of hypoperfusion to the extent that refractory hypotension and acidosis indicate a fatal outcome.

A significant number of patients will show the hyperdynamic profile of increased cardiac output, a decreased peripheral vascular resistance, a decreased arterio-mixed venous oxygen content difference and elevated blood lactate levels throughout the course of their illness.

Adult Respiratory Distress Syndrome (ARDS)

Sepsis remains the most common cause of this acute respiratory complication. Patients are usually hypoxaemic with noncompliant waterlogged lungs. The hypoxaemia is due to a severe ventilation perfusion defect. It is not unusual for the right-to-left shunt to be 30% to 50%. According to Harris the diagnosis can usually be made if:

- PaO_2 < 50 mm Hg on a FiO_2 of 50%.

- The chest x-ray shows diffuse alveolar infiltrates without signs of cardiomegaly or heart failure.

- PCWP < 15 mm Hg.

- The static compliance is less than 50 mL/cm H_2O.

The decreased lung compliance leads to reduced vital capacity and functional residual capacity which increases the work of breathing dramatically. ARDS is discussed in detail elsewhere in the book.

Changes in the Mental Status

Subtle changes occur early in septic shock - even before any change in haemodynamic variables. Symptoms might be irritability, restlessness, confusion, lethargy or disorientation.

Renal Manifestations

Acute tubular necrosis (ATN) is the most common cause of oliguria in patients with septic shock. Typically the urine contains large numbers of tubular epithelial cells, free and in casts, as well as coarse granular pigmented casts. The role of endotoxin and the mediators of sepsis in sepsis-induced ATN is not known, but hypotension and hypovolaemia are usually involved. Renal failure is discussed in detail elsewhere in this book.

Haematologic Manifestations

Sepsis is usually accompanied by a neutrophilic leukocytosis with a "left shift". Overwhelming bacteraemia may cause neutropaenia, especially in the elderly, infants, alcoholics and the immune compromised. Not being able to respond to infection by a leukocytosis is indicative of a poor outcome.

Acute septic conditions do not normally affect red cell number and morphology. However, red cell production is decreased during sepsis and will lead to anaemia if the infectious process is prolonged. Acute disseminated intravascular coagulation (DIC) is a very common complication of serious infection. DIC is characterized by intravascular thrombin generation and fibrin deposition, consumption of clotting factors and platelets, and secondary fibrinolysis. This is a direct effect of vascular endothelial cells. Local nutritive blood flow is decreased by the intravascular microthrombi, and interstitial oedema. Analysis of clotting factors reveal thrombocytopaenia, prolonged prothrombin time and elevated fibrin-fibrinogen degradation products. Patients present with diffuse haemorrhage from mucosal surface, wounds and cutaneous puncture sites. The most important fact to remember about DIC is that treatment of the underlying disease is essential. DIC is a marker for serious infection with a high probability of a fatal outcome. Death is usually due to sepsis and not DIC.

Gastrointestinal Tract Manifestations

Liver dysfunction in extrahepatic intra-abdominal sepsis due to gram-negative bacilli, gram-positive cocci and anaerobes, is a complication seen frequently in the surgical ICU. Patients usually present with cholestatic jaundice which may be secondary to breakdown of red blood cells and hepatocellular dysfunction. Usually there is no necrosis of hepatocytes and parenchymal function remains intact. It appears that hepatic abnormalities are markers of severe illness rather than causes of increased mortality.

Stress ulceration is a condition which occurs within 24 hours of developing sever infection. It consists of painless 1 mm to 2 mm erosions of the mucosa of the stomach and duodenum.

A small percentage of patients may suffer severe blood loss and may require surgery. Concomitant prolonged mechanical ventilation or coagulopathy predispose to serious bleeding.

This condition is also a marked of the severity of the underlying disease.

Diagnosis

Septic shock is essentially a clinical diagnosis, confirmed by culture results. Patients at risk of sepsis should be monitored closely and any trend in their vital signs indicating pyrexia, tachypnoea and tachycardia should be investigated. The importance of meticulous bedside physiologic monitoring cannot be stressed enough. If therapeutic decisions are to be made, monitoring must be accurate. Modern technology has provided us with a wide range of sophisticated electronic monitoring devices, many of which require invasive manipulation. The current impetus is toward the development of noninvasive monitoring equipment. To improve the outcome of critically ill patients, physiologic monitoring must be selected to address those physiologic changes that are pertinent to a specific pathophysiologic state, and to which therapy can be titrated to improve outcome. In shock states, for instance, factors leading to inadequate tissue oxygenation should be monitored. For example, inadequate intravascular volume during hypovolaemic shock, increased afterload after pulmonary embolism and in septic shock inadequate tissue oxygenation due to microcirculatory flow maldistribution. Calculations based on oxygen-derived variables will often show an increased DO_2, a decreased $avDO_2$, decreased oxygen extraction ratio and decreased VO_2. Similarly, in septic shock calculations based of pressure-derived variables may initially show a decreased systemic vascular resistance and an increased pulmonary vascular resistance. Over-reliance on vital signs may lead to significant errors in patient management if the pathophysiology of the underlying disease is not kept in mind constantly. Clinical correlates do predict the presence of sepsis in a significant percentage of patients, but they do so late in the patient's course, since the systemic response to infection has already been initiated.

The principles of monitoring are therefore:

- Select monitoring devices that provide information on which decisions can be made.

- Use noninvasive monitoring preferentially, if available, to minimize the risk to the patient.

- When invasive monitoring devices are used (i.e. Swan Ganz catheter, CVP line, intra-arterial line) sterile technique and catheter care are extremely important.

- Record information obtained frequently and titrate therapy continuously based on trends observed.

- Remove invasive devices as soon as they are no longer necessary.

Table 3.6.16. Guidelines for the Use of Blood Cultures to Diagnose Bacteraemia

1. Adhere to sterile technique.

2. Send at least three sets of cultures (10 mL per set) beginning at the onset of a febrile episode.

3. Vary the site of venipuncture.

4. Never sample from intravascular lines.

5. When the anticipated isolates are also common contaminants, multiple sets should be positive with the same organism for the series to be considered positive.

6. Continuous bacteraemia can be documented by requiring that two or more cultures be positive with the same organism within a series containing multiple samplings.

7. Work closely with microbiology staff. Inform the laboratory of current antimicrobial therapy and use special culture bottles.

8. Estimate the pretest probability of septicaemia, anticipate the causative bacterial pathogen, and interpret the results.

The next important diagnostic effort is an exhaustive search to identify the source of infection, starting with a careful physical examination. Blood, urine and cerebrospinal fluid should be cultured routinely, as well as Gram's stain and culture of tracheal aspirate (table 3.6.16). Care should be taken to deliver viable microbiological samples to the laboratory to ensure optimal results. Potentially infected intravascular lines should be removed immediately and the tips cultured. Abnormal collections of fluid in, for example, the sinuses, empyema, intra-abdominal abscesses, etc should be examined by gram-stain and culture. Often specimens can be obtained by ultrasound directed percutaneous aspiration. Ultrasound is also useful to reveal valvular vegetation. Repeated blood cultures are required to diagnose endocarditis.

Table 3.6.17. Diagnostic Criteria for Nosocomial Pneumonia

1. Onset of purulent sputum production more than 48 hours after admission, with no previous history of pulmonary disease.

2. Pyrexia.

3. New infiltrates on chest radiograph.

4. Physical symptoms and signs of pneumonia.

5. Rise in white blood cell count.

6. Deterioration in oxygenation.

7. Positive sputum culture.

A chest x-ray should be requested if pneumonia or other pulmonary pathology is suspected clinically (table 3.6.17). Patients intubated through the nasotracheal passage, are prone to develop sinusitis which should be diagnosed by x-ray or computed tomography (CT). Intra-abdominal sepsis is often difficult to demonstrate or localize. Ultrasound, isotope studies

or CT scan may be employed to this effect.

While awaiting microbiological results, the diagnosis may be hastened by use of enzyme-linked immunosorbent assays (Elisa) or latex agglutination assays. The limulus amoebocyte lysate test has been suggested as a sensitive indicator of the presence of endotoxin in the circulation. Unfortunately false positive results may occur and a positive result also does not appear to correlate withthe severity of septicaemia.

Although every effort should be made to localise the source and type of infection, diagnostic procedures would not delay prompt treatment of shock state or empiric antimicrobial therapy or definite treatment such as surgical drainage of an abscess. It is important to realise that there is no one indicator, either clinical or laboratory, that is sufficiently sensitive and specific to diagnose sepsis in the postoperative patient.

Management of Sepsis and Septic Shock

According to Young "early clinical suspicion, rigorous diagnostic measures, aggressive initiation of appropriate antimicrobial therapy, comprehensive supportive care and measures aimed at reversing predisposing causes are the cornerstones of successful management". The most important principle in the management of critically ill septic patients is to eradicate the septic focus. Despite the continual development of new broad spectrum antibiotics and their early use in sepsis and septic shock, the mortality rate has not decreased. Many patients die as a result of the pathophysiologic responses to endotoxin even though the antibiotics have sterilised the bloodstream. Zimmerman et al stated that "therapy is therefore aimed at interrupting and reversing the pathophysiologic progression and maintaining organ viability". With all our sophisticated, curative and supportive therapies, we can at best expect to buy time and to manipulate the patient's physiologic milieu in such a way that he will receive the best opportunity to survivie his disease. In this process time is critical - to date, the most effective way to reduce mortality from sepsis, is to treat the infection adequately prior to the onset of septic shock. Because time is critical, empiric treatment is usually required while a more complete diagnostic evaluation is undertaken. Delay in initiating treatment must be avoided at all costs. The management of patients in septic shock is summarized in fig. 3.6.11 and table 3.6.18. Because aspects of the management such as fluid resuscitation, respiratory support, antibiotic therapy, management of haemostatic deficiencies and surgical management of sepsis have been covered externsively in other chapters of this text, this chapter will concentrate on the pharmacotherapy of septic shock.

Table 3.6.18. Guidelines on the Pharmacotherapy of Septic Shock

I Initial Management

1. Resuscitation - "ABC" protocol

2. Restore haemodynamic stability

2.1 Central venous access

2.2 Volume resuscitation

2.3 Inotropic and sympathomimetic agents

3. Broad spectrum antibiotics

4. Monitor vital signs

5. Obtain laboratory specimens

II Specific Management

1. Treat underlying infection or septic focus (repeated surgery as indicated)

2. Support myocardium

2.1 Optimize preload

2.2 Inotropic support

2.3 Decrease myocardial work requirements

2.4 Calcium and magnesium

2.5 Treat haemodynamically significant dysrhythmias

3. Respiratory support

3.1 Oxygen

3.2 Early mechanical ventilation

3.3 CPAP/PEEP

4. Treat biochemical derangements

4.1 Electrolytes

4.2 Glucose

5. Treat hyperpyrexia > 40 °C

6. Treat DIC

6.1 Eliminate cause

6.2 Fresh frozen plasma

6.3 Platelets

6.4 Minidose heparin

III Continuing Management Decisions

1. Reevaluate antibiotic selection when laboratory reports become available or as clinical situation changes

2. Metabolic support

2.1 Enteral nutrition

2.2 Total parenteral nutrition

3. Monitor for signs of MSOF

Fluid resuscitation with a balanced combintation of colloid and crystalloid should be performed aggressively using the fluid-challenge technique to control repletion of the intravascular volume. Invasive monitoring is usually necessary - especially in the elderly. Fresh frozen plasma may also have a place in volume resuscitation both because of its volume effect and the presence of fibronectin, which might be beneficial. In cases with DIC, fresh frozen plasma is essential therapy.

Information gained from gram stains may be of use in the choice of an antibiotic. The choice of antimicrobial drug combinations should be based on the considerations of etiologic agent, site of infection and possible synergism. The latter is very important when treating enterococcus and pseudomonas infections or neutropaenic patients. Increased risk of drug toxicity, superinfection and multiple drug resistance are direct consequences of incorrect antibiotic practices.

Pharmacotherapy of Septic Shock

The sympathetic nervous system is one of the most important compensating mechanisms of the endogenous homeostatic response to sepsis. Norepinephrine is the primary neurotransmitter in the sympathetic nervous system.

The adrenergic receptors are cell surface receptors that mediate the cellular reactions to both endogenous and administered catecholamines and sympathomimetic agents. There are three basic classes of adrenergic receptors, alpha, beta and dopaminergic, and each class can be subdivided into separate categories based on their abilities to bind certain ligands (table 3.6.19). Specific agonists and antagonists react with the receptors to produce specific actions in the vascular smooth muscle, the heart and the kidneys.

Table 3.6.19. Adrenergic Receptors

alpha1	postsynaptic	vascular smooth muscle
vasoconstriction with increased resistance		
alpha2	presynaptic	
stimulation inhibits norepinephrine release (negative feedback)		
beta1	postsynaptic	heart
stimulation	positive inotropy	
	positive chronotropy	
	increased automaticity	
	increased conduction velocity	
beta2	postsynaptic	vascular smooth muscle
stimulation	vasodilation	
	bronchodilation	
	uterine atony	
		bronchial smooth muscle
		uterine smooth muscle
DA1	postsynaptic	renal and mesenteric vascular smooth muscle
		coronary arteries
	vasodilation	
DA2	presynaptic	
stimulation	inhibits norepinephrine and perhaps acetylcholine release	

The approach to a patient with septic shock should include:

- Prompt admission to an intensive care unit.

- Obtaining vascular access for fluid administration and monitoring.

- Assessment of volume status and cardiac performance (fig. 3.6.11).

- Augmentation of stroke volume and cardiac output through fluid administration.

- Collection of appropriate samples of blood, urine, sputum, etc for microbiological analysis. The organism causing the septic shock should be identified as soon as possible.

If volume expansion alone does not result in satisfactory improvement in cardiovascular function, pharmacotherapy is indicated (fig. 3.6.11). Dosages of all drugs must be titrated to effect.

Dopamine

Dopamine is a popular catecholamine frequently used in septic shock. This drug is unique in that its physiologic actions are mediated by alpha, beta and dopaminergic adrenoreceptors. In normal adults at low intravenous infusion rate (0.5-1 microg/kg per min) the physiologic responses observed are mainly dopaminergic and leads to an increased urine output via renal artery vasodilation. The cardiac effects are mediated through beta receptors at rates of 5-10 microg/kg/min. In this range the positive inotropic effect on the heart occurs without a major component of the peripheral vascular effects. Both beta1 receptor stimulation and endogenous release of norepinephrine from myocardial catecholamine stores play a role. Infusion rates greater than 15 microg/kg/min causes alpha receptor mediated effects. All of the selective vasodilation that dopamine causes may be counteracted by the overwhelming alpha-adrenergic effects (table 3.6.20).

Dobutamine

This synthetic catecholamine has a structure similar to isoproterenol. Its major action is inotropic support with dilation of the peripheral vasculature. A complex mechanism of alpha1, beta1 and beta2 receptor stimulation associated with a reflex decrease in sympathetic vascular tone secondary to the increased cardiac output, is responsible for the above-mentioned actions. Cardiac output improves due to an increase in stroke volume. This is accomplished while the left ventricular wall tension and therefore myocardial oxygen consumption decreases. In a condition such as septic shock where the patient has a component of myocardial dysfunction, dobutamine should be beneficial at doses of 2-20 microg/kg/min. The positive haemodynamic effects occurs despite a decrease in cardiac filling pressures, allowing the option of fluid administration. Dobutamine can be added to dopamine with safety during treatment of septic shock. It is the adrenergic drug of choice for low output states because of the improvement in cardiac function with a little increase in heart rate but no increase in myocardial oxygen demand.

Epinephrine

This is one of the endogenous "stress hormones" and is synthesized in the adrenal medulla. Sympathetic stimulation controls its release. Epinephrine has actions mediated by both alpha and beta adrenergic receptors. In the heart the beta1 adrenoreceptors are stimulated, resulting in positive inotropy as well as chronotropy. Beta2 adrenoreceptor binding is responsible for bronchodilation. The vasodilatory response of the vascular smooth muscle is usually seen in skeletal muscle, while the peripheral alpha1 effects of vasoconstriction are observed in the kidney and in the cutaneous vascular bed.

In septic shock a bolus of 2-8 microg IV may be used, or if an infusion is used, the dose is usually in range of 0.015-0.2 microg/kg/min.

Two factors must be considered before administering epinephrine:

- The beta1 effects may increase heart rate to such an extent that patients with preexisting myocardial disease may not be able to tolerate it.

- The alpha 1 effects in the periphery, namely the increase in afterload may cancel the improvement in contractility. For these reasons epinephrine should not be a first line drug used in the treatment of septic shock. A useful combination may be low-dose dopamine to preserve renal perfusion and epinephrine for its alpha and beta adrenergic effects.

Norepinephrine

This neurotransmitter of the sympathetic nervous system, is also useful in the treatment of septic shock, but not available in South Africa at the moment. It is given by infusion at a rate of 0.05 microg/kg/min to more than 0.3 microg/kg/min depending on the effect. Norepinephrine is a potent alpha-2 stimulant resulting in peripheral vasoconstriction. In the myocardium alpha-stimulation produces a positive inotropic effect. Due to a reflex increase in vagal tone there is usually no tachycardia associated with norepinephrine therapy.

In septic shock alpha-adrenoreceptors are down-regulated and binding affinity to the alpha-1 adrenergic receptors is decreased. Despite the concern regarding ischemia of organs, especially in the kidneys, during norepinephrine infusion, a recent study found that this drug increased MAP, SVR and urine output while decreasing HR. It seems that renal perfusion can thus be preserved at commonly-used infusion rates.

Isoproterenol

This is a very potent beta-1 and beta-2 adrenoceptor agonist. Anintravenous infusion can be administered at a dose of 0.01-0.01 microg/kg/min. This increases cardiac output through augmentation of the inotropic and chronotropic mechanisms. Beta-2 stimulation causes vasodilation of skeletal muscle as well as other arterial blood vessels, and also bronchodilation.

Isoproterenol is not recommended for use in shock states unless the patient has a persistent severe bradycardia. When using this drug the intravascular volume must be monitored carefully because marked vasodilation can occur. Beta-1 stimulation also causes tachycardia and increased contractility. In combination with the beta-2 effects myocardial oxygen demand is increased. All these facts together with its arrhythmia potential limit the use of isoproterenol in septic shock to patients with bradycardia.

Phenylephrine

This is an alpha sympathomimetic drug. Its predominant physiologic effect is to increase the afterload of the heart. For this reason it may have little role in the treatment of septic shock, except when the major component of hypotension is due to vasodilation. It may then be used as a short-term vasopressor.

Other Vasoactive Drugs

Amrinone and Milrinone

These are noncatecholamine, nonglycoside inotropic drugs. These drugs act by increasing intracellular c-AMP by inhibition of phosphodiesterase. Amrinone has cardiovascular actions similar to those of dobutamine, and is administered as an IV bolus of 0.75 mg/kg followed by a continuous infusion of 5-10 microg/kg/min. Milrinone is more potent than amrinone and is useful as long-term oral therapy for patients with congestive heart failure who have responded acutely to amrinone. These drugs may be useful for treating shock in patients on chronic beta-blockade because they do not use the beta-adrenoceptor system.

Dopexamine

This is a new synthetic compound which resembles dopamine chemically. Dopexamine is a strong beta2-agonist with only weak beta-1 and no alpha-adrenoceptor agonist activity. It also activates postjunctional dopaminergic receptors with similar equipotency to dopamine. Dopexamine increases cardiac output by increasing stroke volume and heart rate through its inotropic and vasodilating action. A major advantage is the fact that it has no deleterious effects on myocardial oxygen balance and metabolism. This may make it a useful drug in the management of septic shock complicated by severe myocardial failure and increased SVR.

Glucagon

This is also one of the stress hormones and has marked cardiovascular effects. It causes an increase in cardiac index through its chronotropic and inotropic actions. The tachycardia caused by glucagon is not altered by beta blockade but is blocked by verapamil. Although still experimental it has been proposed for treatment of circulatory shock in beta-blocked patients, or in cases which do not respond to conventional therapy. It can be given as a bolus in a dose of 0.01-0.05 mg/kg IV or as an infusion at a rate of 1-3 mg/hour.

Naloxone

This opiate antagonist has been used experimentally in animal as well as human studies, with conflicting results.

It is essential to match the therapeutic effects of the drug or combination of drugs used to the pathophysiologic state of the patient. During the early phase of septic shock most patients will need intravenous volume replacement followed by inotropic support and often vasopressors as well. During the hypodynamic phase some form of afterload reduction may be required additionally. Fig. 3.6.11 outlines the general approach to the management of low perfusion states. The most important considerations in the haemodynamically unstable patient are:

- Obtain accurate monitoring data.

- Maximize intravascular volume - flow work is the least costly in terms of myocardial oxygen consumption.

- Maintain arterial pressure and organ perfusion.

- It is less important which drug or combination of drugs are chosen, than to understand the mechanism, the advantages and liabilities of the drug one selects. Its effect must be monitored carefully to alter or combine pharmacology when ongoing monitoring suggests continued haemodynamic insufficiency.

Experimental Therapies and New Approaches to Septic Shock

Although promising, the widespread acceptance and application of these approaches should always await the results of carefully controlled trials.

Treatment Aimed at Preventing or Antagonizing the Effects of Some of the Mediators Released by the Injured Cell

Corticosteroids

Pretreatment with corticosteroids reduces inflammation and decreases mortality in animals given endotoxin, but they have no beneficial effects in patients if administered after the onset of sepsis and septic shock. On the contrary, if given late, it increases the incidence of nosocomial infection. If the generation of endogenous inflammatory mediators are to be prevented or downregulated, corticosteroids must be given prior to endotoxin.

Prostaglandin E_2

This agent has anti-inflammatory effects on polymorphic leukocytes as well as vasodilating properties which are being investigated with regard to alteration of regional blood flow distribution.

Prostacyclin

This agent's vasodilating properties may improve decreased regional organ blood flow by reversing paradoxical vasoconstriction where vascular endothelium has been damaged. Hypotension is a limiting factor to all vasodilating agents.

Ibuprofen

This nonsteroidal anti-inflammatory agent inhibits thromboxane synthesis and can improve haemodynamic status without affecting metabolic performance (serum glucose and lactate). In sepsis Ibuprofen may therefore be of more use to improve perfusion than to reverse the inflammatory process.

Antioxidant Therapy

Reperfusion injury subsequent to any cause of hypoperfusion results from free radical-mediated injury. Tissue hypoxia increases cellular and extracellular xanthine oxidase levels which promotes formation of toxic oxygen molecules. Xanthine oxidase inhibitors, iron chelating agents, i.e. EDTA and oxygen-free radical scavengers such as mannitol and vitamin

C are being investigated at the moment.

Calcium Channel Blockers

Free calcium influx into the cell is toxic to intermediary metabolism and mitochondrial function. Blocking calcium influx may be cytoprotective. Hypotension in unstable patients is a limiting factor.

Immunotherapy

Immunotherapy of septic shock includes both antibodies to whole organisms and to specific monokines. A comprehensive approach involving selective anti-inflammatory agents and specific antibodies holds more promise than single agent therapeutic regimens.

Monoclonal Anti-TNF Antibodies

Inhibition of the individual pathways of the acute inflammatory response can be accomplished at many points along the inflammatory mediator cascade. TNF appears to be an important primary mediator which is released early during the inflammatory response. Recent animal studies support the hypothesis that anti-TNF antibody administration should suppress the inflammatory response.

Intravenous Immunoglobulin

In a recent review, Berkman et al, stress the importance of immunoglobulins in host defense and central immune regulation. Several intravenous immunoglobulin preparations are available and there is data indicating a useful role in patients with, i.e. primary hypogammaglobulinaemia, idiopathic thrombocytopaenic purpura and bone-marrow transplant patients. Promising results have also been reported in patients with burn wounds. In a prospective randomized study in patients with endotoxaemia and postoperative sepsis, Grundmann observed that adjuvant immunoglobulin reduced mortality and endotoxin titres. These results require confirmation.

Anti-LPS Antibodies

Ziegler et al have shown that human antiserum to E. coli J5, a mutant endotoxin which contains only core determinants, is effective in reducing mortality from endotoxic shock due to a wide variety of gram-negative bacteria. Core LPS antisera are antitoxic rather than antibacterial. When the body's own detoxification mechanisms are exhausted and the patient's own antibodies are consumed, passive immunotherapy is needed conjunction with antibiotic therapy. Monoclonal antibodies seem to offer the most promise. Gaffin found clinically useful high concentrations of anti-LPS antibodies in 7% of donated blood. If the plasma from many such units are pooled, the final product contains mixtures of antibodies capable of binding a wide range of gram-negative bacteria.

Fibronectin

According to Grossman the clinical use of cryoprecipitate or other fibronectin concentrates for prophylaxis or treatment of sepsis cannot presently be supported. Hesselvik suggests that a decreased hepatic rate of synthesis rather than an increased consumption is responsible for depleted fibronectin levels in sepsis. Nevertheless, in a recent study Saba found that the maintenance of plasma fibronectin levels lowered the fluid requirements for haemodynamic support in postoperative septic sheep.

Immune Modulating Drugs

Recent experimental and clinical findings have revealed three approaches to the goal of immune stimulation:

- Substances which influence purine metabolism in lymphocytes to alter theur functional state.

- Histamine H_2 blockers which prevent the production of suppressor T-lymphocytes.

- Natural biological substances produced by immune cells, such as transfer factor, lymphokines (i.e. interferon and IL-2) and granulocyte and macrophage colony-stimulating factor, seem very promising.

Blood Transfusion

It has been shown that multiply transfused patients have markedly reduced natural killer cell activity which is inversely related to the number of erythrocyte units transfused. Transfused patients also have evidence of chronic immunologic stimulation as shown by increased T-cell HLA-DR expression. The immunosuppression seen following transfusions appear to be related to an increased synthesis of prostaglandin E. The use of frozen washed red blood cells that are totally lacking in allogeneic factors may be a method to prevent the immunosuppressive effects.

Resuscitative Techniques and Metabolic Support

These techniques attempt to improve cellular function.

Hyperosmolar Saline

This may act to minimize interstitial and intracellular oedema.

Modulation of Intermediary Metabolism

The multivariable approach to the treatment of shock emphasizes the importance of achieving optimal haemodynamic performance, oxygen consumption and energy generation. Magnesium, ATP, fructose 1,6 diphosphate and dichloracetate are being investigated in this regard. Sagy et al has shown that dichloracetate (DCA) stimulates the oxidative degradation of lactate which is toxic to myocardiac contractility, reduces oxidative phosphorylation and

inhibits glucose use. DCA improves acid-base status, lower high levels of lactate in experimental endotoxic shock and improves haemodynamic performance. This is in contrast to recent evidence that administration of $NaHCO_3$ may be detrimental in the treatment of lactic acidosis.

Modified Alimentation Formulae

Altered fuel sources may function to allow damaged cells to carry on metabolic activity from energy derived from intermediary metabolism. According to Cerra metabolic support in hypermetabolism focuses on protein and nitrogen equilibrium in a setting of reasonable calories with less fat and glucose.

Continuous Arteriovenous Haemofiltration (CAVH)

Unlike conventional haemodialysis, CAVH does not cause a disequilibrium syndrome or episodic hypotension. Larger molecules are filtered suggesting that metabolically active substances such as toxic amines may also be cleared from the circulation.

Thyrotropin Releasing Hormone (TRH)

Holiday et al reports that TRH acts at sites in the CNS as a potent cardiorespiratory stimulant. Additionally, direct actions of TRH at peripheral cardiovascular sites appear to be involved in its pressor and tachycardic effects. These autonomic properties may have potential in the treatment of shock.

Prophylaxis of Sepsis

The ultimate therapy for sepsis should focus on identification of high-risk subsets of patients and preventative measures.

Clinical Assessment of Host Defence

Anergy in surgical patients is a sign of broadly based immune defects, which include abnormalities in specific and local nonspecific antibacterial defences possibly due to an abnormal inflammatory response. The adequacy of host defence in surgical patients can be assessed globally using the delayed-type hypersensitivity (DTH) skin-test response to ubiquitous antigens. Tellado-Rodriguez and Christou make decisions to perform or not to perform major surgery based on the use of the skin test score (the summation of the diameters of induration in five or six tests), as well as the level of serum albumin and the age of the patient. Defining high-risk patients in this way is useful and adds to clinical judgment when planning the perioperative and surgical management of a patient at risk.

Selective Decontamination of the Digestive Tract (GIT)

This is a technique for prevention or treatment of colonization, carriage and subsequent infection in high-risk ICU patients, by enhancement of the defences of the GIT. Van Saene et al have described a triple regimen (selective parenteral and enteral antisepsis regimen, SPEAR) based on this concept. It consists of:

- Selective decontamination of the GIT throughout the ICU stay. A mixture of tobramycin, polymixin E and amphotericin B is applied as a sticky base to the oropharynx and as a fluid via a nasogastric tube to the stomach and distal GIT.

- Cefotaxime IV for the first few days of admission only.

- Intensive microbiological monitoring.

Lactulose

Oral administration of this agent prevents systemic endotoxaemia. A direct antiendotoxic action has also been demonstrated. Pain and Bailey investigated the role of lactulose in preventing endotoxaemia in obstructive jaundice. Their findings suggest that oral lactulose given before operation may be effective in reducing endotoxin-related complications.

Prophylactic Use of Antibiotics

This is discussed elsewhere in this book.

Conclusion

Taking the complexities of the pathophysiology of sepsis into consideration, it is unlikely that any single agent or group of agents will be effective in all patients. In future, investigations of combinations of various agents may produce a "cocktail" aimed at the middle-messenger mediator system or even at the cellular and subcellular levels, which will be able to treat the primary alterations of sepsis and septic shock. Better definition of the pathophysiology of this devastating disease spectrum will be an essential step in the process.

Chapter 3.7: Mechanical Ventilation

A. C. Buys

Introduction

Major progress in contemporary mechanical ventilation can be traced to the need for it in the poliomyelitis epidemic in Los Angeles (1949) and Denmark (1949-1950 and 1952). Major improvements in MV really occurred during World War II, the Korean war and the war in Vietnam. With the Coconut Grove fire in Boston with 39 patients with extensive burns, the first major effort was made to apply to civilian lessons learnt on war casualties. As poliomyelitis declined (Salk and Sabin vaccines) the use of ventilation declined. In 1956 Avery et al advocated the use of tracheostomy and MV for posttraumatic pulmonary insufficiency and flail chest. The first mechanical ventilators were relatively crude and evolved from the negative pressure tank (iron lung) to the progressively more sophisticated positive pressure ventilators (PPV).

MV is a sophisticated addition to treatment and should be conducted in a critical care environment.

Therapeutic Goals

- Adequate arterial oxygenation

- Adequate carbon dioxide elimination

- Reduction or taking over of work of breathing

- Minimal interference with cardiac output

- Prevention of complications

Definition

Mechanical ventilation (MV) is *the mechanical support of air movement into the lungs.* MV provides support for only some of the parameters of respiration.

Indications for Mechanical Ventilation

The main indication for mechanical ventilation are mechanical failure to breathe, disorders of gas exchange and severely raised intracranial pressure.

Mechanical Failure to Breathe

This includes:

CNS Pathology

- Raised intracranial pressure as a result of tumours, subarachnoid-, subdural- or intracerebral haemorrhage, meningitis, abscess, encephalitis and infarction

- Hypoxic brain damage, i.e. postcardiac arrest from near drowning

- Status epilepticus with poor response to anticonvulsants or requiring large doses of anticonvulsants

- Pathology in the region of the brainstem (tumour, thrombosis and haemorrhage)

- Cervical cord pathology (trauma, haematoma, infarction and tumour)

- Drug overdose "Ondine's curse"

- Amyotrophic lateral sclerosis

- Polyneuropathy as a result of a critical illness

Neuromuscular Disease

- Poliomyelitis, Guillan-Barre syndrome and myasthenia gravis

- Axonal degeneration of motor and sensory nerves has been held responsible for a polyneuropathy which occurs as a complication in at least 50% of patients with sepsis and multiple organ failure for longer than two weeks.

Drugs and Poisons

- Anaesthetic-, sedative- and anticonvulsant overdose.

- Prolonged neuromuscular blockade as a result of overdosage or altered muscle relaxant action or as part of the therapeutic regimen (i.e. tetanus).

- Organophosphate poisoning.

- Bulbar and peripheral paresis due to snake bite (Black and Green Mambas; Cape, Egyptian and Forest Cobras; occasionally the Berg Adder).

Mechanical Abnormalities of the Thorax

- Viral and bacterial pneumonia, pulmonary oedema, pulmonary embolism, pulmonary contusion.

- Flail chest (associated with lung contusion and impaired gas exchange).

- Kyphoscoliosis.

Disorders of Gas Exchange

- Infantile respiratory distress syndrome (hyaline membrane disease).

- Adult respiratory distress syndrome (ARDS).

- Chronic lung disease - emphysema, chronic bronchitis, bronchiectasis, pulmonary interstitial fibrosis especially when associated with an acute complication, i.e. pneumonia.

- Bronchospasm unresponsive to conservative therapy.

- Cardiac disease - left-ventricular failure with pulmonary oedema, pulmonary hypertension, right-to-left intracardiac shunting.

Incipient Ventilatory Failure

In diverse conditions such as the ARDS, lung contusion, herpes simplex encephalitis, severe cerebral trauma (where the development of cerebral oedema is expected to occur), and multiple injuries where the patient is coping at the time of examination, but where increased

work of breathing is becoming evident and there the chances are that, in spite of adequate conservative treatment, the patient's condition is going to get worse before it is going to get better, it is infinitely better to initiate MV before the patient develops ventilatory failure.

Major Surgery

Mechanical ventilation is also indicated in some patients after major surgery if the chances for the development of postoperative respiratory failure are high. These include major cardiac or pulmonary surgery; thoraco-abdominal surgery; neurosurgical procedures, especially if cerebral oedema is expected to develop, and postoperatively in patients with multiple injuries especially if pain relief would necessitate the frequent use of high-dose potent narcotics.

Muscle Fatigue

Patients with disorders of gas exchange as well as patients with peripheral paresis or bulbar paresis often develop associated respiratory muscle fatigue creating a vicious circle with escalating decompensation of respiratory function. These patients are often very anxious, which increases O_2 requirements, further compromising ventilation. Narcotics and sedatives are contraindicated because of aggravation of muscle weakness or depression of respiration. If muscle weakness is noticed in a patient where rapid improvement of the cause of the weakness is unlikely with treatment, MV should be instituted beforfe ventilatory decompensation commences, since severe hypoxia can occur very rapidly. Muscle weakness not only involves movement of air in and out of the lungs, but is also associated with inability to cough up secretions, which further compromises ventilation.

Criteria

The generally accepted criteria for the institution of MV in previously eucapnic individuals, are:

- Vital capacity < 15 mL/kg

- Inspiratory force < - 20 cm H_2O

- PaO_2 (FiO_2 = 1.0) < 300 torr

- $PaCO_2$ > 50 torr

- VD/VT > 0.6

- Respiratory rate > 35 breaths per minute and anxiety.

The above criteria are late signs and relate to severe deterioration in respiratory function. Adjustments should therefore be made according to the pathology responsible for the respiratory failure and the course it is expected to take.

Increased work of breathing as reflected by a steadily rising respiratory rate with

utilization of accessory respiratory muscles, in spite of treatment, should be considered an indication for ventilatory support. The increased work of breathing, apart from increasing oxygen demand, leads to respiratory muscle fatigue as well as increased cardiac work. The initial improvement with mechanical ventilatory support may lie as much in the reduction of oxygen demand as in a rise in oxygen supply.

Another sensitive and important indicator for ventilatory support, is progressive decrease of arterial oxygen tension with or without abnormalities of arterial carbon dioxide tension.

MV should be instituted in patients with certain abnormal breathing patterns (i.e. central hyperventilation, Cheyne Stokes breathing) indicative of severe cerebral pathology, without waiting for actual respiratory failure to develop.

Severe cerebral oedema, as such, is an indication for controlled MV. Lowering of the arterial pCO_2 (within physiologically acceptable levels) reduces cerebral blood volume, thereby reducing brain bulk and intracranial pressure. In these patients cerebral parameters rather than respiratory, are the indications for MV. (Under no circumstances should a patient with intracranial hypertension be allowed to strain or cough on the endotrachea tube, since this would lead to marked increases in intracranial pressure.)

In patients with certain neuromuscular diseases such as the Guillan Barré syndrome, weakness of the respiratory muscles may be associated with weakness or absence of the cough reflex as well as an inability to swallow. Accumulation of secretions and aspiration may occur with resultant pulmonary pathology. Respiratory muscle fatigue can actually worsen the degree of paralysis.

Once a combination of factors occurs - respiratory muscle weakness, pulmonary pathology as a result of accumulation of secretions and aspiration - deterioration to an irreversible state can be startingly rapid. In conditions such as these, for which there is no rapid cure, MV should be started before the classical signs of respiratory failure develop and before pulmonary pathology develops.

Ventilators

Mechanical ventilators can be broadly classified into negative-pressure devices and positive-pressure devices.

Negative-Pressure Ventilators

The iron-lung - one of the earliest forms of mechanical ventilatory support available - was described in 1929 by Drinker and McKhann. It is a large box enclosing the body of the patient, with a minimal seal around the neck, leaving the head exposed to ambient pressure. Ventilation occurs when an electrically driven motor powering a bellows generates negative pressure within the box surrounding the patient. Part of the negative pressure is transmitted through the chest wall, producing a pressure gradient between the patient's mouth and the alveoli so that gas flows into the lungs.

The cuirass ventilator surrounds only the trunk of the patient but functions on the same principle as the iron lung.

Negative-pressure ventilators have largely been replaced by positive-pressure ventilators but may still be useful in the longterm management of some patients with neuromuscular disease and respiratory insufficiency.

Choice of ventilatory support will depend on:

- Whether full or partial support is necessary.

- Existing or pre-existing pulmonary disease.

- Other system pathology.

- Complications versus benefits of alternative techniques.

Classification of Positive-Pressure Ventilators

Most of the classifications of ventilators are according to the phase of the mechanical ventilatory cycle.

Inspiratory Phase

Inspiratory gas flow occurs when a pressure gradient between the proximal airway and alveoli (Paw-Pa) is established. Two primary mechanisms are utilized to generate mechanical tidal volume (V_T) and ventilators are classed either as flow or pressure generators although no commonly employed ventilator functions entirely as one or the other. The inspiratory phase may be static or dynamic.

Flow Generators

Constant-flor generators (CFG) produce gas flow at a uniform rate despite changes in pulmonary mechanics. Flow generator output usually assumes one of 4 wave forms with a constant (square wave), sinusoidal accelerating, or a decelerating pattern.

In order to maintain uniform flow regardless of airway pressure (Paw) a CFG must be powered by a high-powered gas source. The larger the gradient between the CFG working pressure and the Paw, the less likely it is that any changes in the patients compliance or resistance will alter the flow characteristic of the ventilator.

Nonconstant flow generators (NCFG) produce gas flow rates that vary throughout inspiration with the variability constant from breath-to-breath.

Flow generators incorporate injectors, pistons, on/off solenoid valves, servo-controlled solenoid valves or servo-controlled stepper-motor valves.

- Injectors are functionally based on the Bernoulli and Venturi principles (Bird Mard

series ventilators, IMV, IMV Bird; Puritan-Bennett MA-1, MA-2; Engstrom Erica).

- Piston pumps are positive-negative displacement devices moving a specific volume of gas with each stroke (Engstrom ER 300; Emerson 3 PV, 3 MV).

- On/off solenoid valves are used in conjunction with a high pressure gas source to generate inspiratory flow.

- Servo-controlled solenoid valves are used in some microprocessor operated ventilators.

- Solenoid valves are used in the Bear-1; Bear-2; Puritan-Bennett 7200; Ohmeda CPU1.

- Servo-controlled stepper motors have the stepper motor insufflation valve incorporated into the ventilator (Siemens servoventilators; Bear-5).

Automatic flow supplementation of servo-controlled inspiration may be of value in managing patients with labile ventilatory drive and inspiratory V_T demand during assisted mechanical ventilation.

Static flow generators: During a selected time interval the exhalation valve is held closed after gas flow has ceased and V_T has been delivered, producing a nondynamic (no flow) component of mechanical ventilation, end-inspiratory plateau (EIP).

The rationale for EIP is based on the fact that variations in pulmonary time constants (airway resistance x pulmonary compliance) between lung compartments prevents homogeneity of gas distribution. Lung units with relatively high resistance will fill slowly (slow spaces) and those with lower resistance will fill more rapidly (fast spaces). EIP promotes redistribution of gas from fast to slow spaces.

Pressure Generators

- Constant pressure generators sustain a uniform pressure throughout the inspiratory phase regardless of changes in pulmonary mechanics.

- Nonconstant pressure generators develop variable pressure throughout inspiration with the pressure pattern remaining the same from breath to breath, regardless of alterations in pulmonary mechanics.

Changeover from Inspiratory to Expiratory Phase

Termination of the inspiratory phase can be volume-cycled, time-cycles, flow-cycled or pressure-cycled.

Volume-cycled ventilators terminate the inspiratory phase following delivery of a pre-selected volume of gas to the ventilator circuit. A portion of this volume is lost by distention of and compression within the ventilator and breathing circuit. The "lost" volume is dependent

upon the volume and compliance of the entire ventilator-patient circuit and the peak inspiratory pressure. Thus the volume delivered by a ventilator and that actually received by the patient may differ considerably under varying clinical conditions.

Time-cycled ventilators terminate the inspiratory phase after a preselected time interval has relapsed. Ventilatory cycling phases are determined by manipulating one or more of the following: inspiratory and expiratory time; inspiratory and total ventilatory cycle time; or inspiratory and EIP time as a percentage of total cycle time. The VT delivered by time-cycled ventilators is determined by the inspiratory time (T_I) and inspiratory flow rate (V_I).

Pressure-cycled ventilators terminate the inspiratory phase when a preselected pressure is achieved within the ventilator circuit. At this point, inspiratory gas flow ceases and a valve opens allowing exhalation. V_T and inspiratory time (T_I) are directly related to pulmonary compliance (CL) and inversely to airway resistance and circuit impedance.

Significant leaks in the circuit or at the airway prevent development of the requisite inspiratory cycling pressure. Nearly all volume-, time-, and flow-cycling ventilators can be adjusted to terminate inspiration at a preselected pressure.

Flow-cycled inspiration is terminated when the gas flow rate decreases to a predetermined level. This mechanism is employed by microprocessor-based ventilators offering inspiratory pressure support (PS) modes.

Expiratory Phase

Mechanical expiration commences when the exhalation valve opens. Pressure may return rapidly to baseline (atmospheric) level or the valve may be depressurized gradually to provide resistance (retardation) to exhalation. It may also open until the circuit pressure decreases to a preselected positive level, at which point it again closes to maintain the pressure - positive end-expiratory pressure (PEEP).

Expiration is usually a passive event facilitated by a positive alveolar-to-ambient pressure gradient resulting from lung-chest-wall recoil. Expiration time depends on the magnitude of the gradient and airway resistance (including resistance from ET and ventilator tubes). Reduction of circuit pressure during the expiratory phase speeds up expiration. If it is maintained only until ambient airway pressure is restored, expiration is accelerated, but lung volume does not decrease below FRC, and intrapleural pressure does not fall below its resting level. If a subatmospheric circuit pressure develops (negative end-expiratory pressure - NEEP), lung volume falls below FRC and intrapleural pressure decreases beyond its normal end-expiratory level. Significant reduction in NEEP is associated with atelectasis and hypoxaemia. It was originally introduced to neutralize the haemodynamic effects of PPV but its disadvantages outweighed its advantages.

Retardation of expiratory gas flow rate decreases the slope of the expiratory pressure curve and may prevent premature airway collapse and air trapping in patients with obstructive pulmonary lesions. Apart from obstructive lung disease, the most common cause of air trapping is iatrogenic and involve excessive ventilator cycling rate and/or V_T. Persistent pulmonary hyperinflation is associated with an increased incidence of pulmonary barotrauma,

hypercapnia, reduced venour return and increased pulmonary artery pressure.

Alveolar Closure and Alveolar Collapse

During expiration the largest decrease in alveolar volume occurs in the dependent lung regions so that airways and alveoli collapsew first in the dependent regions. Patients with a high risk for developing alveolar atelectasis are those with decreased lung compliance (pulmonary oedema, ARDS), with decreased FRC (elderly patients, postoperatively especially after thoracic or abdominal surgery, endotracheal intubation, ARDS) and with an increase in closing volume (extreme age, chronic obstructive airway disease).

Any factor which brings the FRC level nearer to the closing point, increases the likelihood of atelectasis during expiration. MV as such, has no beneficial effect on this relationship. Techniques utilizing positive pressure during the expiratory phase (i.e. PEEP, CPAP) keep the FRC level above the closing point, thus preventing basal airway and alveolar collapse in high risk cases.

Collapsed alveoli do not expand immediately when a ventilator cycles to the inspiratory phase. Instead, a variable period of time is required before the alveolar critical opening pressure (COP) is reached. When COP is achieved and inspired volume is added, alveolar recruitment occurs. As pressure decreases during expiration the critical closing pressure (CCP) which is lower than COP, is reached and collapse recurs. The duration of alveolar expansion is unpredictable.

Positive End-Expiratory Pressure (PEEP)

PEEP is produced by maintaining a residual positive pressure during the mechanical expiratory phase. When the patient's expiratory pressure equals the preset PEEP, exhalation ceases and the lungs remain inflated at an increased volume. PEEP is applied in an attempt to minimize the airway and alveolar collapse associated with, for instance ARDS, bronchospasm and diffuse areas of atelectasis, and to increase FRC so that a bigger area is exposed to gas exchange in the alveoli.

Various therapeutic endpoints for PEEP therapy have been proposed. "Optimal PEEP" is generally referred to as the PEEP value that reduces Qsp/Qt to 0.15 or less with the concomitant maintenance of normal cardiovascular function. The "best PEEP" technique seeks the greatest improvement in pulmonary compliance. Suter and colleagues equated optimum PEEP with optimum lung function as shown by maximum oxygen transport (cardiac output x arterial oxygen content) and the lowest dead space fraction. They used the expression "best PEEP" to equate with maximum oxygen transport. "Best PEEP" in their patients corresponded with the point of maximum lung compliance and was 0-15 cm H_2O.

Other investigators found that maximum compliance and maximum oxygen transport do not coincide at the same level of PEEP in the majority of patients. It is apparent that criteria for application of PEEP based on achieving maximal oxygen delivery will not necessarily include the level of PEEP necessary to optimize pulmonary blood-gas exchange. "Prophylactic PEEP" had been advocated in the treatment of patients with a high probability of developing ARDS in the hope that early application of PEEP prior to the development of

severe hypoxaemia, may reduce morbidity and mortality.

PEEP is only one of the variables that can be adjusted to improve oxygenation. The others include fractional inspired oxygen (FiO_2), Vm, and the inspiratory:expiratory ratio. Since high inspired oxygen concentrations may cause direct oxygen toxicity, the FiO_2 is kept below 50-60% whenever possible. PEEP reduces cardiac output and tissue perfusion, causes diversion of pulmonary blood flow, increases lung water, reduces urinary output, increases the risk of barotrauma and increases intracranial pressure. Wolff and colleagues found that all levels of PEEP decrease cardiac output to such an extent that the increase in arterial oxygen tension does not prevent a reduction in oxygen transport.

The most practical way to use PEEP is as advocated by Albert - using the lowest level of PEEP that maintains an adequate PaO_2 on an FiO_2 of less than 50-60%.

Maintenance of adequate circulation is achieved by infusion of crystalloids and colloids as well as inotropic agents. Inotropic agents, i.e. dopamine, increases shunting which, however, is eliminated by PEEP.

Gallagher, Civetta and Kirby defined optimal PEEP in terms of a predetermined goal of a reduction in pulmonary shunt to 15% or an increase in the PaO_2/FiO_2 ratio to over 300. They suggested incremental increases in PEEP until those goals were achieved using fluid infusion and inotropic support to maintain cardiac output. Actually the aim in critically ill patients should be to manipulate ventilation as well as circulation in such a way that oxygen consumption is not limited by impaired oxygen transport.

In patients with severe chronic airway obstruction (CAO) on MV the rate of lung emptying is slowed by the high expiratory resistance and by expiratory flow limitation. The time available between two mechanical inflations is therefore often inadequate for the completion of expiration and end-expiratory pressure remains above zero. This is termed "auto" PEEP or "intrinsic" PEEP (PEEPi). PEEPi can also be present in critically ill, mechanicaly ventilated patients with acute respiratory failure due to various aetiological factors without a history of chronic airway disease.

Changeover from Expiratory to Inspiratory Phase

Mechanical ventilators may change from the expiratory to inspiratory phase by one or more of the following modes: assist, control, assist-control and IMV. The changeover can be time, pressure, or flow cycled.

- Time-cycled controlled exhalation is used in IMV and high frequency ventilation (HFV) techniques. The duration between breaths is time dependent and unaffected by patient effort.

- Pressure-cycled termination of expiration results from a decrease in airway pressure caused by the patient's inspiratory effort. It is independent of time.

- Flow-cycled changeover occurs when exhalation is terminated by flow-cycling with a pneumotachometer sensing a patient-triggered 0.1 litre/second flow rate.

Assisted Ventilation

Ventilators capable of assisted (patient-triggered) ventilation incorporate mechanisms that respond to a decrease in airway pressure, caused by the patient's spontaneous breathing effort, and switch to the inspiratory phase. The response sensitivity pressure necessary to trigger a mechanical breath is usually adjustable by means of a sensitivity control.

Controlled Ventilation

Continuous mandatory ventilation (CMV) provides ventilation predetermined entirely by the machine settings. It guarantees a specific minute ventilation (Vm) and indications include CNS pathology, drug overdose, post-anaesthetic depression, neuromuscular disease and severe ARDS.

Hypnotic and narcotic drugs with, when necessary, neuromuscular blocking drugs and hyperventilation of the patient to a $PaCO_2$ below the apnoeic threshold are often used to coordinate the patient and the ventilator by overruling the patient's respiratory rhythm. Hyperventilation produces respiratory alkalosis which may cause increased oxygen consumption, decreased cerebral blood flow, increased systemic vascular resistance, decreased cardiac output, increased airways resistance, decreased pulmonary compliance and a shift to the left of the oxyhaemoglobin dissociation curve. These changes may potentiate underlying problems of oxygen uptake, delivary and utilization. Animal experiments also indicated an acceleration in lactate production in hypocapnic hypoxaemia compared to eucapnic or hypercapnic hypoxaemia. In humans lactic acidosis is seen in patients with severe midbrain injuries with central hypocapnic hypoxaemia.

Assisted-Controlled Ventilation

Many ventilators provide assisted, controlled and assisted-controlled modes of ventilation. When used in combination, the control rate is set slightly lower than the current patient-triggering frequency. If the patients stops breathing the ventilator will convert to CMV at the back-up rate.

Intermittent Mandatory Ventilation

This was originally introduced in 1971 by Kirby and colleagues to treat infants with hyaline membrane disease and by Downs and associates for use in adults. IMV allows spontaneous breaths between ventilator breaths. The set mechanical ventilatory rate (the IMV breaths) cannot be influenced by the patient. Between sequential mechanical breaths, an unrestricted flow of gas equal to or greater than the patient's peak inspiratory demand must be provided to minimize spontaneous work of breathing.

Synchronized IMV (SIMV) has been incorporated into ventilators to prevent "stacking" of mechanical breaths upon spontaneous ones. In SIMV, the patient triggers the mandatory V_T at regular intervals similarly to assisted ventilation, but breathes spontaneously between the mandatory V_T. There are no proven advantages of SIMV over IMV. Advantages of IMV are lower mean airway pressure and therefore less depression of venous return and CO.

The incidence of barotrauma is less and requirements for sedation are less. The IMV rate is set to keep the pH and blood gases normal with spontaneous breaths less than 30.

There are, however, still many indications for CMV, mainly in patients with CNS pathology as well as patients where there is increased work of breathing (with its concomitant increased oxygen demand and consumption) on IMV.

Continuous Positive Airway Pressure (CPAP) and

Spontaneous Positive End-Expiratory Pressure (sPEEP)

CPAP and sPEEP are positive pressure modes used with spontaneous breathing. With CPAP, both inspiratory and expiratory pressures are positive, although the inspiratory level is less than the expiratory level. With sPEEP, airway pressure is zero or negative (subambient) during inspiration, but increases at the end of expiration to a predetermined positive pressure. Both CPAP and sPEEP are designed to increase expiratory transpulmonary pressure and lung volume (FRC).

Early in the course of acute respiratory failure the patient is hypoxic but initially usually eucapnic or hypocapnic, requiring correction of the hypoxaemia. In relatively mild cases CPAP or sPEEP can be employed to alleviate the condition.

Poorly designed CPAP systems as well as deterioration of the pulmonary pathology can increase inspiratory work and lead to a fatigued patient.

Pressure Support (PS) Ventilation

Ventilators, i.e. the Bear 5 and Siemens 900C include PS modes that operate in conjunction with their demand-flow valves. Work of breathing is decreased by PS. In the PS mode, the ventilator is patient-triggered "on", continuing in the inspiratory phase to a preselected positive pressure limit. As long as the patient's inspiratory effort is maintained, the preselected airway pressure stays constant, with a variable flow of gas from the ventilator. Inspiration cycles off when the patient's inspiratory flow decreases to a preselected percentage of the initial peak mechanical inspiratory flow. The ventilator thus is flow-cycled in the PS modes, after which passive exhalation occurs.

A low level of PS can be employed as "assisted mechanical ventilation" between IMV breaths, to decrease spontaneous ventilatory work or the PS level is adjusted to provide the desired V_T and minute volume.

Mandatory Minute Volume (MMV)

The patient is guaranteed a preselected minute volume. If the entire amount is breathed spontaneously, ventilator augmentation does not occur. If not, that portion of the preselected minute volume which is not breathed spontaneously is delivered by the ventilator automatically. MMV is incorporated in the Bear 5, the Hamilton Veolar and the Ohmeda CPU 1 ventilators.

High Frequency Ventilation (HFV)

HFV is defined as ventilation of the lungs at a frequency which is equal to or greater than four times the normal physiological range. The aim of the technique is to produce low-peak airway pressures by the use of small tidal volumes. There are three subclasses of HFV: high-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV) and high-frequency oscillation (HFO).

HFPPV (1-2 Hz) and HFJV (1-5 Hz) share common ventilator characteristics and differ mainly in the connection to the patient. Tidal volumes are generated by opening and closing the outflow from a pressurized air/oxygen gas source using a fluidic, mechanical or electro-magnetic valve. The duration of inspiration is usually fixed between 20% and 40% of each cycle. Expiration is passive. The patient connection used with these two techniques differs in its potential for entrainment of ambient gas during HFJV. The diameter and therefore cross-sectional area of the orifice through which fresh gas reaches the airways is larger with most techniques of HFPPV (3-5 mm ID) than the jets which are used with HFJV (1.6-2.0 mm ID). Consequently gas at a given flow rate is discharged into the trachea at a higher velocity with HFJV.

HFO (3-40 Hz) operates on the principle of cyclical pressure changes applied to the trachea by connecting a piston pump or the cone of a loudspeaker directly to the patient's endotracheal tube. The gas in the airways is thus oscillated to-and-fro at high peak rates. Time available for expiration decreases, there is insufficient time for expiration and lung volume increases with hyperinflation of the lung (a type of "auto" PEEP).

Definite indications for HFV are:

- Difficult intubation.

- Bronchoscopy and laryngoscopy.

- Laryngeal and tracheal operations.

- Bronchopleural fistula.

- Tracheo-oesophageal fistula.

- HFJV has also been explored as an alternative to one-lung ventilation in thoracic surgery.

Possible other indications are hyalie membrane disease and emergency percutaneous transtracheal jet ventilation for conditions such aas acute upper-airway obstruction, i.e. crushed larynx. Complications are mainly inadequate humidification, tracheal mucosal damage as a result of shear forces from the high-velocity jet pulses, auto PEEP and has outflow obstruction.

Apnoea may or may not be produced by HFV. Respiratory effects also include lower mean adn peak airway pressures and more negative pleural pressures, there is therefore less

danger of barotrauma and CO is maintained. Unexplained metabolic acidosis has occurred after prolonged HFV.

HFPPV

Low compliance ventilator which delivers small volumes at frequencies of 60-120/min. Total Vm may be more than normal.

HFJV

A high-pressure jet pulses gas down the airway at volumes 1-3 times the anatomical dead space. Additional gas is entrained to augment the volume delivery.

HFOV

There is no net displacement of gas, but a continuous movement of the same volume of gas in and out of the airway. A separate source of O_2 must be provided into the circuit.

Physiological Changes

Cardiac Output (CO)

Venous return to the right atrium is determined by the effective venous inflow pressure, which is the pressure gradient between the extrathoracic and the intrathoracic venous pressures. MV impedes venous return during inspiration and PEEP impedes venous return during expiration with decreased right atrial and ventricular filling and consequent decreased filling of the left heart and decreased cardiac output (CO). The degree of impairment is accentuated in the presence of a negative fluid balance.

O_2 Delivery and Consumption

MV usually increases O_2 delivery. A severe fall in mean arterial pressure as a result of MV, however, can lead to decreased O_2 delivery as well as increased pulmonary venous admixture. PEEP usually increases PaO_2 with improved O_2 delivery as well as decreasing venous admixture provided CO is not significantly depressed.

MV usually diminishes O_2 consumption by taking over the work of breathing from the respiratory muscles. O_2 consumption may be increased if an injudicious respiratory alkalosis is allowed to develop.

Cerebral Blood Flow and Intracranial Pressure

Hyperventilation increases cerebral vascular resistance and decreases cerebral blood flow with a decrease in intracranial pressure. A mild drop in CO may be advantageous especially if the arterial pressure is high as a result of the raised intracranial pressure.

If cerebral perfusion is critical (marked intracranial hypertension or cerebral vasospasm) a decrease in arterial pressure may lead to capillary collapse and cerebral

ischaemia. PEEP impedes venous return with a resultant incre3ase in cerebral venous and intracranial pressures. This effect can be counteracted to some extent by nursing the patient in the anti-Trendellenburg position provided the mean arterial pressure is within acceptable limits.

Fluid Balance

MV causes a fall in glomerular filtration rate, renal blood flow, as well as sodium and water clearance. There is therefore a tendency for patients on MV to develop water retention and oedema. Several factors may be responsible for this:

- Decreased CO with impaired renal perfusion.

- Redistribution of renal blood flow from the cortex to the medulla.

- Stimulation of the volume receptors with increased renin and aldosterone secretion (decreased intravascular volume in the intrathoracic veins, pulmonary vessels and atria interpreted as hypovolaemia).

- Increased ADH secretion and reflex mechanisms via the baroreceptors in the aortic arch.

Acid-Base Balance

Judicious MV corrects respiratory acidosis but injudicious hyperventilation causes respiratory alkalosis with the following detrimental effects:

- A shift of the oxyhaemoglobin dissociation curve to the left with increased affinity of haemoglobin for O_2 resulting in tissue hypoxia.

- Increased airway resistance.

- Cerebral vasoconstriction and decreased cerebral perfusion.

- Decreased CO due to unfavourable tissue pH.

- Decreased ionized calcium, phosphate, magnesium and potassium.

- Increased rate of glycolysis and O_2 consumption.

- Decreased sensitivity of the respiratory centre.

- Lactic acidosis (type A) occurs as a result of tissue hypoxia resulting in anaerobic metabolism and increased lactic acid production. Tissue hypoxia in this instance is the result of vasoconstriction and reduced tissue perfusion. Lactic acidosis has negative effects on myocardial failure.

Monitoring

Visual observation by experienced clinicians and nurses remains the primary and most essential form of monitoring. Monitoring includes V_T, respiratory rate, PIP, FiO_2 and inspired gas temperature: pH, arterial blood gases, blood count, chest radiography, monitoring of respiratory mechanics, such as static compliance of the total respiratory system, and diverse other investigations as required by the patients pathology.

Minimal ventilator monitoring alarms include high and low pressure modules, electronic and/or pneumatic power failure indicators and a failure-to-cycle detector.

Weaning from Mechanical Ventilator

Weaning should start when there is reversal of the primary pathological process, cardiovascular stability, pulmonary function measurements that appear compatible with spontaneous ventilation and a favourable clinical impression of the patient's status. An assessment should also be made regarding residual effects of narcotics and sedatives and relaxants.

Methods of weaning patients from mechanical ventilatory support include IMV and T-piece trial of spontaneous ventilation. T-piece trial involves periodic disconnection of the patient from the ventilator and delivery of humidified oxygen/air via a T-piece. Each successive period off the ventilator is increased until the patient is weaned. Weaning on IMV involves a gradual (1-2 breaths at a time) decrease of mechanical breaths, provide pH, pO_2 and pCO_2 remain within acceptable levels and provided the patient does not tire. The patient should be extubated while still on PEEP (5 cm H_2O). Clinical assessment, blood gases and pulmonary function indicate the speed with which the patient can be weaned. Failure to wean from the ventilator may be due to:

- Residual pulmonary pathology.

- Inadequate cardiopulmonary function.

- Muscle weakness as a result of polyneuritis.

- Narcotic and sedative depression.

- Malnutrition in debilitated patients may result in respiratory muscle weakness.

- Atrophy of the respiratory muscles may develop as a result of prolonged CMV.

- Hypophosphataemia.

- Psychological dependence on the ventilator. Apart from dependence, insecurity and anxiousness can increase oxygen demand beyond the patient's ventilatory capabilities.

- Excessive glucose intake and parenteral alimentation can increase CO_2 production beyond the patient's ventilatory capabilities.

Complication of Mechanical Ventilation

Oxygen Toxicity

Retrolental Fibroplasia (RLF)

Exposure of neonates (especially with low birth mass) to high concentration of oxygen, causes constriction of the retinal vessels with severe ischaemia and blindness.

Pulmonary Damage

Breathing oxygen at concentrations of 50% or less or breathing 100% oxygen for less than 24 hours cause no damage to the lungs. Prolonged breathing of or ventilation with oxygen concentrations higher than 50% cause changes in the lung resembling the pathological changes found in ARDS. The partial pressure of inspired oxygen rather than FiO_2 is responsible for the degree of the pulmonary injury.

Initially a tracheobronchitis develops. Between 48-72 hours endothelial swelling and interstitial oedema progress further, areas of capillary and alveolar endothelium become denuded followed at approximately four days by necrosis of type I pneumocytes with marked increase in interstitial fluid volume and leukocyte infiltration. At this stage lung compliance is decreased and gas transfer compromised. The outcome may be fatal. If corrected in time, complete recovery can take place or pulmonary fibrosis may result. Clinical and pathological manifestations of oxygen toxicity are similar to that of ARDS.

Atelectasis

When breathing air or being ventilated with an O_2/air mixture, nitrogen has a "splinting" effect on the alveoli.

When lung units with perfusion in excess of ventilation are ventilated spontaneously or mechanically with high concentrations of O_2, nitrogen is washed out of the alveoli, oxygen combines with desaturated haemoglobin faster than it is replaced, leading to collapse of the underventilated alveoli (absorption atelectasis). This occurs in patients with acute as well as chronic respiratory pathology. Peribronchiolar oedema and secretions tend to be worse in the dependent portions of the lung with absorption atelectasis therefore most common in these areas. When breathing spontaneously, ventilation is preferentially distributed to the dependent lung regions but with MV the non dependent areas are the better ventilated, which also contributes to atelectasis developing in the dependent lung region.

Hyperventilation

Excessive alveolar hyperventilation causes hypocapnoea with a shift of the oxygen dissociation curve to the left, decrease in cerebral blood flow and an increase in peripheral vascular resistance.

Hypoventilation

Hypoxaemia and/or hypercapnia can occur as a result of the lung pathology or as a result of mechanical malfunction. Hypoventilation as a result of inadequate VT will also predispose to the development of atelectasis in dependent lung regions.

Decreased Cardiac Output (CO)

CO decreases during MV, especially in combination with PEEP. The degree of depression is accentuated if there is depletion of intravascular volume.

The decreases in tissue perfusion and O_2 delivery, if uncorrected, can be a contributing factor to the development of multiple organ failure.

Pulmonary Barotrauma (BT)

Barotrauma in association with MV occurs over a wide range of mean airway pressures. The incidence increases with peak inspiratory pressure requirements above 40 cm H_2O.

The main factor predisposing to the development of pulmonary barotrauma is the severity of the pathological process in the lungs. Infection, especially pulmonary infections, as well as hyaline membrane disease and ARDS are definite risk factors. Tissue necrosis may play an important causative role.

The severity of the damage to the lungs will determine the degree of decrease in compliance and gas exchange. As compliance decreases, the lungs are exposed to higher peak inspiratory pressures during MV. MV at high frequencies apparently also increases the risk of barotrauma.

Hypovolaemia predisposes to the development of barotrauma since an increase in the intra-alveolar pressure and volume leads to a decrease in blood vessel volume which is accentuated in hypovolaemic states, increasing the pressure gradient between the alveoli and the vessels. With an increase in alveolar pressure and volume, and its concomitant decrease in blood vessel volume, traction occurs on the alveolar wall at the point of blood vessel attachment. Alveolar rupture occurs when a critical traction force is exceeded. Air would then enter the perivascular sheath resulting in PIE.

Pulmonary interstitial emphysema (PIE), defined as extra-alveolar air dissecting within the interstitium of the lung - may progress further, dissecting to the hilar areas and the facia plane of the neck, face and thorax with the development of subcutaneous emphysema (which for a time can serve as a reservoir preventing the development of a tension pneumothorax), pneumothorax, pneumomediastinum, pneumopericardium and even pneumoperitoneum.

In the presence of MV, these complications are more life-threatening than during spontaneous breathing, since the application of positive pressure very rapidly leads to the development of a tension pneumothorax with deleterious effects on ventilation as well as haemodynamics with a fatal outcome if an immediate decompression is not carried out.

Although a rare occurrence, tension penumopericardium is similarly potentially fatal complication if pericardiocentesis is delayed.

The pathogenesis of pneumopericardium (PPC) and pneumoperitoneum is unknown. Tension PPC is associated with a high mortality rate unless promptly treated (pericardiocentesis).

Subcutaneous emphysema, especially of the neck and face is usually more frightening to the patient and his relatives than dangerous. However, especially with high PEEP levels, it can progress to tension subcutaneous emphysema which have been reported to cause tracheal obstruction.

Tension subcutaneous emphysema has also been implicated in the development of intracranial hypertension. The elevated subcutaneous pressure may cause extrinsic compression of the internal jugular veins in the soft tissues of the neck, leading to cerebral venous congestion and intracranial hypertension.

Cannulation of the superior vena cava via the subclavian vein or, more rarely, the internal jugular vein, may be complicated by puncture of the lung with a resultant pneumothorax which in the presence of positive pressure ventilation (PPV) can progress very rapidly to a life-threatening tension pneumothorax. Radiographic manifestations of PBT include mediastinal emphysema, subcutaneous emphysema, small parenchymal cysts, halos of air surrounding the pulmonary vessels, subpleural air dissection, frank air cysts, pneumothorax, pneumopericardium and pneumoperitoneum.

Clinical evaluation, seriual chest radiographs, as well as an awareness of the possibility of barotrauma developing is necessary for timely intervention.

The reported incidence of barotrauma is 4-18%. If possible a chest radiograph should be taken to confirm the diagnosis of a pneumothorax (or other forms of barotrauma). If the ventilation and circulation is severely compromised temporary relief can be obtained by inserting a large gauge (no 15) intravenous cannula attached to a syringe in the second intercostal space (antero-laterally) and decompressing the lung temporarily.

Positioning of the patient is important since a small pneumothorax can be missed if the x-rays are taken with the patient in the supine position. In the upright position, the air tends to collect over the apex of the lung, provided there is no trapping of air due to other pulmonary disease. In the critically ill patient it is often not possible to take the x-rays in the upright position and the clinician should therefore be on the lookout for the altered distribution of air in the pleural space. In the supine patient air collects in the anterior costophrenic sulcus with hyperlucency over the upper abdominal quadrants and over the anterior costophrenic sulcus.

After placement of the tube, control radiographs should be taken to assess re-expansion of the lung. A loculated tension pneumothorax can occur in patients on MV in spite of the presence of an intercostal drainage tube and requires additional treatment.

Pneumomediastinum occurs infrequently. Mediastinal air is usually decompressed by

leaking into the subcutaneous tissues (subcutaneous emphysema) or into the thorax (pneumothorax) or into the peritoneum (pneumoperitoneum). Intrathoracic scarring or scarring in the neck may prevent escape and decompression of the mediastinal air and a tension pneumomediastinum may occur, compromising venous return and leading to cardiovascular collapse. If not heavily sedated, the patients may complain of chest pain, there is congestion of the neck veins, Hamman's sign ("mediastinal crunch") may be present and there may be electrocardiographic changes. Mediastinal decompression is then indicated - a small incision is made approximately 2-3 cm above the suprasternal notch and opening the deep fascia beneath the sternum (adults) and insertion of a fine catheter into the anterior mediastinum (infants).

Pneumopericardium may develop as a rault of mediastinal air decompressing into the pericardium, presenting with the signs of cardiac tamponade and requiring pericardiocentesis.

Measures to decrease pulmonary barotrauma include:

- Decreasing ventilator frequency.

- Preventing coughing or straining on the endotracheal tube by means of sedatives and relaxants.

- Adjusting PEEP, FiO_2 and V_m for optimal ventilation but attempting (within acceptable blood gas values) to minimize peak airway pressure.

- Maintenance of normal intravascular volume (blood, water and electrolytes and albumin).

- Independent lung ventilation in selected cases.

- Decreasing peak inspiratory flow.

Infection

The development of sepsis in patients on mechanical ventilation (MV) is an always present danger and accounts for most of the deaths in patients on MV after one week. In spite of major advances the infection rate has remained essentially unchanged. Most patients requiring MV for longer than a few days are critically ill and catabolic. There is failure of more than one vital organ system, with impaired defence against infection. The patients often require invasive techniques for monitoring and therapy, thus increasing the risk of infection. The infection rate is directly correlated with the duration of treatment: after one week, the infection rate increases to over 80%.

Infections may be bacterial, viral or fungal and include sinusitis, nosocomial pulmonary infections, cystitis, vaginitis, septicaemia, suppurative thrombophlebitis. Cellulitis following on nasal necrosis may lead to sinus cavernous thrombosis.

The pathogenesis of nosocomial pulmonary infection appears to be related to oropharyngeal as well as intestinal colonization followed by the aspiration of organisms.

Apart from serving as a pathway for organisms, endotracheal tubes have been shown to act as a reservoir for potential pathogens. The molecular cement, the glycocalyx, attaches micro-organisms to inert surfaces and, apparently, to endotracheal tubes. Organisms were cultured from the scrapings of endotracheal tubes and it has been suggested that detachment and aspiration of such aggregates from the endotracheal tube may constitute a reservoir for persistent contamination of the tracheobronchial tree.

Aspiration Pneumonitis

Aspiration can occur past an endotracheal or tracheostomy tube causing exacerbation of the lung damage.

Stress Ulceration

The incidence of stress ulceration in patients on MV is directly related to the severity of the patient's pathology. The severity of the ulcerations range from superficial mucosal erosions to deep infiltrating ulcers and may be confined to the stomach or duodenum or may involve the entire gastrointestinal tract. Increasing the pH of the gastric contents toabove 3.5-4.0 reduces the incidence.

Although continuous intragastric feeding raises the pH, it is insufficient to provide adequate ulcer prophylaxis, and pharmacologic gastric acid neutralization is required in patients at risk.

Unfortunately alkalinization of the gastric contents contribute to micro-organism colonization of the stomach, increasing the incidence of nosocomial respiratory infections.

Sucralfate, a drug which protects the gastric mucosa without significantly increasing the pH, has therefore been proposed as the drug of choice for decreasing the incidence of stress ulceration without increasing the danger of nosocomial infection.

Other Abdominal Complications

Massive gastric distension may occur although this is probably more often the result of hypoxia than MV. Causative or contributory factors for the delayed gastric emptying of the stomach and ileus which so often occur in patients on MV, may be the pathological process as such, or may be the result of heavy sedation.

Necrosis of the gallbladder is a rare complication in patients on long term MV. Poor perfusion, cholestasis and gall stones may be contributing factors.

Complications of Endotracheal Intubation and Tracheostomy

These include injury to the lips, nose, teeth, pharyngeal mucosa, larynx and trachea. Subluxation of the mandible has been described. With nasotracheal intubation dissection of the mucosa of the nasopharynx may lead to the development of subcutaneous emphysema. Laryngitis and tracheitis are frequent complications.

Airway obstruction due to kinking or obstruction of the tube, accidental extubation, misplacement of the tube, intubation of a main stem bronchus or movement of the tube into the bronchus due to inadequate fixation, with resultant atelectasis and intrapulmonary shunting in the nonventilated lung, can occur all too easily. Nasal necrosis, tracheal stenosis or tracheomalacia, arytenoid ulceration, intubation granuloma with persistent hoarseness, oesophagotracheal fistula, oral and tracheo-bronchial ulceration are possible later complications. Klein describes complete loss of mucosa down to the cricoid in a hypotensive infant intubated for only 6 hours.

Airway obstruction due to laryngospasm and/or supraglottic or epiglottic oedema can complicate the immediate post extubation period, especially in infants.

Aspiration of gastric contents may occur on extubation since pressure of the cuff transmitted through the posterior wall of the trachea may cause a blockage with slow accumulation of regurgitated gastric contents in the oesophagus which may enter the pharynx on deflating the cuff.

Predisposing factors for laryngotracheal damage are:

- Mucosal ischaemia due to prolonged intubation

- Overinflation of the cuff

- Infrequent release of cuff pressure

- Too large a tube

- Systemic hypotension

- Chronic airway infection

- Actions increasing movement of the cuff and tube within the trachea will occur if the patient strains and coughs on the tube or is fighting the ventilator because of inadequate sedation. Movement also occurs when turning the patient, with movements of the neck or traction on the ventilator tubes and during suction

- Repeated intubations and extubations, especially accidental extubation with an inflated cuff

- Attempts to pass too large a tube

- Poor design of the endotracheal tube.

Prevention of damage include:

- Meticuluous attention to every aspect of intubation - choice of type and including the correctly sized tube and well designed endotracheal and tracheostomy tubes and cuffs

- Low-pressure, high-volume cuffs

- Inflation pressure of the cuff below capillary perfusion pressure

- Flexible catheter mounts and swivels to reduce transmission of movements to the larynx and trachea

- Gentle intubation technique, stabilizing the tube and supporting the tube during movements and suctioning

- Adequate sedation to prevent straining and coughing as well as restlessness and decorticate and decerebrate posturing

- Utilizing relaxants if sedatives are inadequate

- Attempts at speech should be discouraged

- Aseptic techniques

- Adequate humidification of inspired gases.

Ventilator Complications

These include machine malfunction, alarm failure, inappropriate machine settings and poor design.

Chapter 3.8 Pulmonary Aspiration

A. C. Buys

Aspiration of Gastric Contents

Aspiration of gastric contents occurs far more frequently than generally recognized.

Five to fifty percent of postoperative deaths related to anaesthesia are said to be due to aspiration pneumonitis. Aspiration pneumonitis takes one of two clinical forms:

- Aspiration of undigested food that has been vomited or regurgitated. The clinical picture is one respiratory distress and obstruction by particulate matter.

- Acid aspiration pneumonitis, caused by the inhalation of gastric secretions with a pH of less than 2.5 (described by Mendelson in 1946 in obstetrical patients - Mendelson's syndrome).

The features of aspiration pneumonitis are similar to the changes occurring in the ARDS.

Cardiopulmonary resuscitation (CPR) as such can cause aspiration of gastric contents.

Gastric insufflation is a frequent and dangerous complication of ventilation with an unprotected airway. High inflation pressure and/or incorrect positioning of the head with partial upper airway obstruction will increase the risk.

The frequency of acute dilatation of the stomach is unknown. The majority of cases occur as a result of hypoxaemia or following surgery or major trauma. Other associated conditions include acute severe infections, diabetic ketoacidosis and stress. It is less common since the widespread use of nasogastric tubes and continuous drainage of gastric contents. Whatever the cause, the stomach rapidly distends with gas and mucosal secretions leading to an increase in intragastric pressure. If the condition is not recognized early and rectified by the passage of a nasogastric tube and drainage of the gastric contents, there is a very real danger of aspiration.

Blood

Aspiration of blood is less serious unless the volume inhaled is excessive or mixed with gastric secretions as in patients with haemorrhage from the intestinal tract.

Hydrocarbons

Ingestion of hydrocarbons such as kerosene and petrol cause respiratory failure combined with CNS irritability.

Near Drowning

Pulmonary changes occur with aspiration of salt or fresh water and depend on the amount of water aspirated. 12% of patients do not aspirate because of laryngospasm or breath-holding.

Predisposing Factors in the Occurrence of Aspiration

Adbominal distension and GIT pathology:

- Late pregnancy
- Obesity
- Ileus
- Intestinal obstruction
- GIT haemorrhage
- Hiatus hernia
- Gastric atony
- Oesophageal diverticulae

- Ca of the oesophagus, stomach.

Trauma

Delayed gastric emptying or ileus occur with all trauma but especially with cerebral, cervical-cord and abdominal trauma.

Severe Sepsis

Obtunded cerebration:

- Cerebral pathology: injury, infarction and infection

- Epilepsy

- Drug overdose

- Coma, i.e. insulin coma, hypoglycaemic coma.

Depression of the cough and/or swallowing reflexes include:

- Parkinson's disease and other extrapyramidal disorders

- Bilateral corticobulbar tract lesions causing pseudobulbar palsy

- Midbrain encephalitis

- Lower motor neurone lesions of the IX, X and XII cranial nerves (with bilateral vagal paralysis food and fluid is regurgitated into the pharynx and nose on swallowing)

- Guillan Barré syndrome

- Posterior fossa tumours and infarction

- Myasthenia gravis

- Vocal-cord paralysis

Nasogastric Feeding

Artificial airways

- Endotracheal tube

- Tracheostomy

Snake bite

- Cobra and mamba venom are neurotoxic causing interference with swallowing, coughing and breathing due to muscle paralysis

Diagnosis

A history of vomiting or regurgitation in a patient with respiratory insufficiency would suggest the diagnosis. However, in a number of patients there is no history of regurgitation or vomiting. The presence of gastric contents or bile in the hypopharynx or airways when the patient is being intubated or suctioned, will confirm the diagnosis. In 37% of patients aspiration is silent or unwitnessed.

Approximately 88-94% of patients who aspirate, develop pulmonary infiltrates on chest x-rays (fig. 3.8.1) which may develop within hours or be delayed for 12 to 24 hours.

Prevention of Aspiration

Awareness

In order to prevent aspiration from taking place the clinician should be aware that it is an ever present danger.

It is not always sufficiently appreciated that even fairly minor trauma or surgery, anaesthesia, narcotics, stress, fear and hypoxia - can cause significant delay in emptying of the stomach. With anaesthetic and narcotic administration in patients requiring pain relief or surgery, there are the added factors of possible nausea, depression of cerebration and upper airway obstruction.

Pilots have a saying about airline disasters: "it's none or a crowd", and the same principle often applies in medicine. When major medical disaster occur, there is often a sequence of mishaps.

Narcotics

The dose of narcotics administered for the relief of pain should be tailored to the patient's age, physiological status and degree of pain. Although adequate pain relief is essential, a few simple measures could decrease narcotic requirements significantly. These include: making the patient as comfortable as possible, keeping the surgical patient warm in theatre and putting the patient in a warmed bed, limiting movement from trollies and beds, regional blocks, local anaesthetic infiltration of wounds and administering analgesics with less depressant effects on cerebration and respiration and with a lower incidence of nausea and less depression of gastric motility (such as dihydrocodeine and pentazocine). Maintenance of consciousness is of paramount importance.

Positioning

Patients with obtunded cerebration should whenever possible be nursed on their sides.

Clear Airway

Respiratory obstruction frequently causes reflux of gastric contents into the oesophagus.

Endotracheal Tubes

In adults cuffed ET tubes that pass easily, but with a diameter large enough to require only small volumes of air in the cuff to prevent an air leak, should be used. High-volume, low-pressure cuffs, cause least damage. Pressures should not be above 25 to 34 cm H_2O. Awake intubation should be considered in some of the patients at risk. In patients on positive pressure ventilation the use of PEEP also prevents aspiration of secretions from above the cuff.

Nasogastric Tubes

The passage of a nasogastric tube is essential in patients with suspected ileus or delayed gastric emptying. Although gastric emptying is incomplete, there is at least reduction in the volume of gastric contents with lessening of the danger of regurgitation. On should keep in mind that the presence of a nasogastric tube does not eliminate the danger of aspiration. If emergency surgery is contemplated, the stomach is emptied via the nasogastric tube and the tube then removed just prior to induction. The continued presence of the tube may increase the risk of active regurgitation or may act as a wick through the oesophageal sphincters to allow silen reflux of gastric contents into the hypopharynx.

Restriction of Intake

Intake of fluids and food should be stopped in patients if delayed gastric emptying is a possibility or where bowel sounds are reduced or absent. Sufficient time should be allowed before surgery for gastric emptying. When an anaesthetic has to be given to a traumatized patient, the time interval between food intake and time of injury rather than between food intake and surgery - should be considered.

Metoclopramide

Gastric emptying can be facilitated by the administration of the drug, metoclopramide, although it is not to be depended on.

Anaesthetic Procedure

The indication for the so-called "crash" induction technique is facilitation of intubation in patients considered likely to vomit or regurgitate during induction of anaesthesia. It entails pre-oxygenation followed by the use of an ultra-short-acting IV induction agent and a muscle relaxant, with rapid intubation with a cuffed endotracheal tube utilizing the Sllick manoeuvre

(cricoid pressure) to prevent passive regurgitation. Suctioning apparatus should be kept handy. A small dose of a non-depolarizing relaxant prior to succinylcholine administration will prevent muscle fasciculations (which may contribute to an increase in intragastric pressure) if succinylcholine is to be used.

In order to prevent regurgitation, steep head-up positioning of the patient prior to induction has been proposed. This may lead to a precipitous fall in blood pressure in patients with an unstable circulation as well as increased difficulty with the intubation. Therefore the horizontal recumbent position is usually preferred.

Protection of the Airways

Consciousness should be maintained if possible. Narcotics and sedatives should therefore be used judiciously in patients at risk and patients nursed on their sides whenever possible.

Patients with depressed cerebration have a high risk of aspiration since the laryngeal reflexes and the cough reflex may also be depressed. There is a high incidence of ileus in unconscious patients especially during the acute phase of cerebral pathology. Later on, with tube feeding, the possibility of aspiration still remains high. With polyneuropathy or pathology involving the brainstem, obtundation of the cough and the swallowing reflexes may cause inability to protect the airways. Endotracheal intubation or tracheostomy may become necessary to protect the airways in these patients as well as in some unconscious patients. Endotracheal tubes that are large enough to prevent an audible air leak in children would reduce the incidence of aspiration past the endotracheal tube. Utilizing PEEP if the patient is on positive pressure ventilation decreases the incidence of secretions leaking past the cuff.

Antireflux procedures such as Nissen fundoplication may be required if conservative measures to prevent reflux, fail.

Alkalinization

Alkalinization of gastric contents with antacids has been advocated, but particulate antacids can actually increase the danger of injury to the lungs.

Since histamine H_2 blockers inhibit the secretion of gastric acid elicited by histamine or other H_2 agonists (both the volume and the hydrogen ion concentration) in a dose-dependent, competitive manner, cimetidine and ranitidine has been used to decrease gastric acid secretion before surgery or parturition. Proton pump inhibitors of which omeprazole is a prototype, cause a more profound reduction of gastric acid secretion and may also become useful in this context. Metoclopramide may be of value in patients at risk. Its mode of action is two-fold: an anti-emetic effect because of a central antidopaminergic action at the chemoreceptor trigger zone and a peripheral action stimulating acetylcholine release causing increased gastrointestinal motility, increased lower oesophageal sphincter tone and decreased pyloric tone. Apart from controlling nausea and vomiting it hastens gastric emptying, and therefore gastric volume, with less danger of regurgitation. It also significantly decreases the duration of postoperative delayed gastric emptying or ileus if no other complicating factors are present.

Okasha, Motaweh and Bali administered cimetidine (400 mg) 3-4 hours before induction or 20 mg magnesium trisilicate 1-2 hours before induction or a combination of both drugs to patients scheduled for elective Caesarian section. They found that many patients may be endangered by having a large volume of acid gastric juice and that all the therapeutic regimens employed were useful although the combined use of cimetidine and magnesium trisilicate was most effective. The use of cimetidine (4 mg/kg) and metoclopramide (0.15 mg/kg) administered IV in 50 mL saline 30 minutes before surgery was assessed by Solanki, Suresh and Ethridge. The results indicated that cimetidine raised the pH, but did not decrease gastric volume. Metoclopramide decreased gastric volume as well as raised the pH, although the latter effect was less than that of cimetidine. The effects of the drug combination were additive. The implication is that the use of the combination reduces the risk of aspiration pneumonitis.

Increasing the pH of the gastric contents to above 3.5-4.0 reduces the incidence and with a pH of 5.0 or more, no stress bleeding was seen in a study undertaken by Valentine, *et al.*

Treatment

Bronchial Lavage

Alkaline bronchial lavage has been tried and found to be detrimental. Suctioning for removal of secretions and small particulate matter should be performed routinely.

Bronchoscopy

Bronchoscopy should only be performed if large particulate matter has been inhaled. Apart from bronchoscopy for the removal of particulate matter, the treatment is essentially similar to that of ARDS as a result of other causes.

Antibiotic Therapy

Prophylactic antibiotic therapy is unnecessary in cases with mild aspiration and minor clinical signs. Although many investigators advocate the withholding of antibiotics until clinical evidence of infection develops, the prognosis worsens markedly if infection is superimposed on an already injured lung. Antibiotic therapy is therefore indicated if ARDS develops or if faeculent material has been inhaled.

Bronchodilators

Especially with acid aspiration, patients may develop bronchospasm in which case bronchodilators are administered via a nebulizer or intravenously.

Corticosteroids

Controversy exists about the appropriateness of cortisone therapy for aspiration syndromes. To suppress the inflammatory response, administration has to be initiated within hours of the aspiration occurring. However, there have been several reports that

corticosteroids may interfere with healing.

Chronic Aspiration

Patients with chronic aspiration usually present with recurrent pneumonia or interstitial lung disease of undetermined aetiology. Mostly patients with neurological disease or with injury affecting glottic closure are involved.

According to Goodwin the incidence of pneumonia in patients receiving nasoenteral feeding whose tracheas are not intubated, is 5.7-13%. In adult ICU patients intubated with low-pressure, high-volume cuffed ET tubes, it is 20% and 15-17% with low-pressure, high-volume tracheostomy tubes. It increases to 77% in infants and children and to 80% in neonates if uncuffed ET tubes are used.

It also results from gastro-oesophageal reflux associated with the presence of a feeding tube especially if associated with delayed emptying of the stomach or high volume feeds.

Near-Drowning

After near-drowning, information regarding the circumstances surrounding the incidence is important:

- Saltwater or fresh water

- Contaminated water

- Approximate period of hypoxia

- Hypothermia

- Presence of alcohol or drugs

- Head injury, spinal cord injury, myocardial ischaemia?

- Had cardiac arrest occurred?

- Resuscitation - degree of skill; delay before initiation of resuscitation.

Emergency management should proceed according to the principles of cardiopulmonary resuscitation. The pressure necessary to inflate the lungs of the near-drowned victim is greater than for someone apnoeic from nonpulmonary causes. Lung compliance is reduced after aspiration and may be extremet with aspiration of contaminated fluid.

The patient may passively regurgitate and aspirate swallowed water and gastric contents. Vomiting of large volumes of water and gastric contents often occur when the patient begins to respond. Immersion hypothermia predispose to ventricular fibrillation and asystole (temperature below 28 °C) and to unsuccessful resuscitation. Conversely core temperature below 30 °C may afford some protection to the brain.

- Laryngeal spasm may occur when immersed and may prevent aspiration of water.

- Electrolyte estimations should be done as soon as possible and corrections carried out.

- Hypothermic patients should not be warmed.

- A nasogastric tube should be passed and gastric contents drained.

- Measures should be instituted to minimize and treat cerebral oedema in patients with signs of hypoxic cerebral damage. These include prevention of techniques that may increase cerebral metabolism or cerebral blood volume; (gentle handling, minimal painful stimuli, prevention of pyrexia), positive pressure ventilation; administration of dexamethasone (0.1 mg/kg 8 hourly) - although steroids may not be as effective in cytotoxic (hypoxic) cerebral oedema as in oedema associated with cerebral neoplasms; administration of long-acting and short-acting barbiturates in order to lower cerebral metabolism although the results of these are equivocal at best; administration of lignocain and hypothermia.

Induced hypothermia ios being used in many centres. Once again the results are equivocal and may cause complications. In most patients the better course would probably be to maintain normothermia. Prophylactic antibiotics are essential as are measures to prevent stress gastrointestinal ulceration. Seizures may occur and should be controlled by anticonvulsants.

Complications are the complications of ARDS as well as complications of cerebral oedema and obtunded cerebration. Fixed dilated pupils and the occurrence of seizures are poor prognostic signs.

Chapter 3.9: The Adult Respiratory Distress Syndrome

A. C. Buys

Introduction

For many years a lung condition that very often led to fatal ventilatory insufficiency has been identified in association with quite a number of vastly dissimilar pathological states. However, the clinical and pathological manifestations are sufficiently similar to consider the condition as a single entity - the adult respiratory distress syndrome.

The ARDS is par excellence an example of Morgagni's view that severe illness affects the whole body, though its life-threatening manifestations may be most obvious in one or more organs.

Definition

The ARDS is a diffuse but nonhomogeneous inflammatory lung disease caused by many inciting aetiological factors, due to either direct or nonspecific injury to lungs, usually previously normal, at the alveolar-capillary level leading to increased permeability resulting

in an increase in extravascular lung water, which is essentially non-cardiogenic, and which is characterized by respiratory distress, hypoxaemia, reduced pulmonary compliance and lung infiltrates on x-rays.

History

Acute respiratory failure was identified in batlefield casualties in World War I. Most severely traumatized patients did not live long enough to develop respiratory insufficiency and the few who were resuscitated after severe shock often died rapidly from what at that time, was called posttraumatic massive pulmonary collapse.

With advances in medical care a large number of World War II and Korean was casualties did survive long enough to develop, what then was called the traumatic wet lung or blast lung. During the Vietnam was, with rapid evacuation of casualties as well as haemodialysis for the treatment of renal failure, increasing numbers of repiratory complications were seen after thoracic as well as non-thoracic trauma. This frequently fatal condition was called the Da Nang lung. At the same time a similar pathological condition was seen in civilians in association with, for instance, hypovolaemic states, aspiration of intestinal contents and bacterial and viral infections. This was called congestive atelectasis, respirator lung, pump lung, stiff-lung syndrome, traumatic wet lung, shock lung, etc.

In 1967 Ashbaugh and colleagues described respiratory failure in 12 patients characterized by dyspnoea, tachypnoea, non-compliant lungs and lung infiltrates with diverse aetiologies. As a result of the similarity to the infant respiratory distress syndrome (hyaline membrane disease), the term ARDS was later used by these investigators.

Etiology

The clinical manifestations and pathological findings of ARDS are similar, irrespective of the cause of the condition. However, individuals with similar acute illnesses do not all develop ARDS. The reasons for only some patients developing the syndrome are largely unknown.

There are certain conditions that are associated with the development of ARDS.

Pulmonary or Systemic Sepsis

ARDS may develop with pulmonary as well as systemic sepsis and may occur with Gram-negative as well as Gram-positive infections. Septic shock is a common precursor of ARDS. It has also been described in association with miliary tuberculosis. Legionnaires' disease, fungal and viral diseases, as well as malaria and other protozoal diseases.

Hypovolaemic States

- endotoxaemic shock

- anaphylactic shock

- haemorrhagic shock

- shock as a result of severe fluid and electrolyte loss in patients with burns. There may be the added factor of inhalation of hot or toxic gases.

Trauma (Thoracic and Non-Thoracic)

This occurs most often in patients with multiple injuries, fractures of long bones, crush injuries and direct injury to the lungs.

Complicating circumstances that are often present and increase the possibility of ARDS developing are hypovolaemic shock, aspiration of gastric contents and multiple blood transfusions.

Fat Embolism

Occurs most often in association with fractures of the long bones.

Neurological Disorders

Patients with cerebral pathology, especially if there is associated raised intracranial pressure (i.e. head injuries, subarachnoid haemorrhage, acute hydrocephalus and seizures) can rapidly develop pulmonary oedema. The causal mechanism is though to be intense central sympathetic stimulation causing a shift of blood from the systemic to the low-resistance pulmonary vascular bed with resultant pulmonary hypertension, hypervolaemia and increased pulmonary capillary permeability.

Pulmonary oedema may also develop in the absence of increased systemic or pulmonary artery pressures which raises the possibility of the presence of another mechanism causing increased pulmonary alveolar permeability, since it has been found that virtually all patients who sustained severe head injuries have elevated lung-water volume.

Complicating factors increasing the possibility of development of pulmonary oedema are often present in patients with cerebral pathology especially in the presence of raised intracranial pressure and/or obtunded cerebration. Regurgitation with aspiration of gastric contents is an ever-present danger.

Partial airway obstruction with laboured breathing in patients with depressed cerebration, causes a marked increase in negative intrathoracic pressure which, in combination with the elevation of peripheral pressure, would increase the possibility of pulmonary oedema developing as well as aggravate the degree of oedema.

Aspiration of Gastric Contents

Aspiration, especially if the aspirated material has a pH of less than 2.5, can lead to the development of ARDS. Aspiration of particulate matter, stagnation fluid with a higher pH and meconium (neonates) can also cause ARDS.

Near Drowning

Heat Stroke

Air Embolism

Macrothromboembolism and Microthromboembolism

Peripheral venous thrombi, fat or tissue or tumour emboli can cause release of vasoactive substances.

Disseminated intravascular coagulation (DIC) may be the cause of ARDS developing or may complicate ARDS.

Obstetrical Emergencies

- Amniotic fluid embolism

- Eclampsia

- In-utero foetal death

Inhalation of Toxic Agents

Acid fumes, i.e. pool acid (HCL), chlorine, ammonia, sulphur dioxide, phosgene, smoke and toxic fumes from burning plastic.

Iatrogenic Miscalculations

Oxygen Toxicity

Oxygen carries a distinct risk of damaging pulmonary tissue. The clinical picture is similar to that of the adult respiratory distress syndrome (ARDS). Cell damage results from the intracellular production of O_2 metabolites and O_2 radicals such as hydrogene peroxide, superoxide radicals and hydroxyl radicals. It is unlikely to develop with inspired O_2 tensions below 50% or 100% for less than 24 hours. The degree of damage is related to the partial pressure of inspired O_2 and not the FiO_2. Oxygen toxicity may also be a complication exacerbating the lung lesion in ARDS patients on mechanical ventilation.

Incompatible Blood Transfusion Reactions

This causes lysis of the erythorcytes with release of thromboplastic agents as well as activation of the complement cascade and other vasoactive systemic mediators which may trigger the development of ARDS.

Over-transfusion of blood especially in the presence of impaired renal function can cause this reaction.

Overhydration and hypoalbuminaemia can exacerbate the capillary leakage in ARDS.

Massive Blood Transfusion

High-Altitude Hypoxia (High-Altitude Pulmonary Oedema)

Major Surgery

Especially organ transplants and open heart surgery.

Pancreatitis

Uraemia

Radiation Pneumonitis

Narcotic Drug Abuse

Especially heroin and methadone. In some of these patients aspiration of gastric contents may be a complicating factor.

Other Drugs and Poisons

Barbiturates, ethclorvynol, salicylates, chlordiazepoxide, colchicine, dextran 40, propoxyphene, thiazides and paraquat. Paraquat toxicity produces an acute lung injury by a mechanism that involves the production of superoxide radicals.

Bowel Infarction

Disseminated Carcinomatosis

Immune Disorders

Goodpasture's Disease

Acute Vasculitis

Haematologic Disorders (HD)

Therapeutic advances in the management of severe HDs have increased survival time, but simultaneously impaired host defences predisposing HD patients to opportunistic infections and other complications such as ARDS. The development of ARDS can initially be mistaken for lung infiltrates due to drug toxicity or *vice versa.*

Mechanism of Lung Injury Leading to ARDS

ARDS develops as an acute, widespread, pulmonary microvascular injury caused by substances delivered to the lung by either the airways or the circulation and leading to leakage of fluid across the alveolar-capillary membrane. The protein concentration of the oedema fluid is higher than in patients with cardiogenic pulmonary oedema. Although the precise mechanism triggering the injury is uncertain, the origin is probably multifactorial.

Activation of vasoactive substances causing widespread vasodilatation and increased permeability, leading to capillary-alveolar leak is probably responsible for the initial injury.

Despite intensive research, the precise mechanisms underlying the increased capillary permeability are still largely unknown and it is unclear whether damage to the capillary endothelium is the initial injury which results in ARDS. The lung injury is accompanied by many cellular and biochemical processes: some may initiate the syndrome, others may perpetuate the syndrome and still others may inactivate the byproducts of inflammation. The appearance of the ARDS during the course of certain illnesses is supposed to be partly the result of intrapulmonary neutrophil sequestration and degranulation induced by inflammatory mediators. Such activation products could be produced either through release from a local site of injury or by undefined and possibly disease-specific intravascular processes.

Complement Activation and Neutrophil Sequestration

"Complement" is a collective term to describe a system of about 20 different proteins which are normally present among the plasma proteins. Many of these are enzyme precursors and are normally inactive. They can be activated in two separate ways, the classical pathway and the alternate pathway.

The classical pathway is activated by an antigen-antibody reaction setting into motion a cascade of sequential reactions.

The alternate pathway can be activated in response to large polysaccharide molecules in the cell membranes of some invading micro-organisms. These substances react with complement factors B and D, forming an activation product that activates factor C3, setting off the remainder of the complement cascade beyond the C3 level. The alternate pathway is one of the first lines of defence against invading micro-organisms.

Some of the effects of activated complement are:

- Enhancement of opsonization and phagocytosis by the neutrophils and macrophages - factor C3b

- Leuko-attraction causing migration of neutrophils to the lung and accumulation in

the lung - factor C5a

- Activation of mast cells and basophils with release of histamine and other vasoactive substances into the local fluids - C3a C4a and C5a

The endpoint of the complement cascade is the lytic complex - C5b6789 with a direct effect on cell membranes causing lysis or rupture of cells, i.e. micro-organisms.

Histologic studies of the lung have demonstrated extensive trapping of granulocytes in the pulmonary vasculature and interaction between neutrophil granulocytes and the complement system has been proposed as a central pathophysiological mechanism in ARDS.

There is also lysis of the neutrophils. With the rupture of their cell membranes toxic vasoactive products are released. These include proteolytic enzymes, superoxide radicals, lyzosomes, elastase and collagenase. Elastase and collagenase cause destruction of basement membranes and the proteolytic enzymes activate the Hageman factor and complement, and split fibrinogen.

Complement activation is not unique in ARDS, but is also observed in patients at risk for (but without the development of) ARDS. The development of pulmonary injuryt therefore seems to be a consequence of the **intensity** of the local inflammatory reaction rather than a specific pathophysiologic inflammatory event.

Activation of Eosinophyls

Activated complement components are also eosinophilotactic. Although patients with ARDS have been reported to have a total peripheral eosinopenia, they do show a marked increase in circulating levels of eosinophil cationic protein (ECP), a specific constituent of eosinophil granulocytes. It has been postulated that the cytotoxic products of eosinophil degranulation may be involved in the development of organ lesions in ARDS.

Some patients with ARDS fail to demonstrate pulmonary neutrophil aggregation histologically. In a comprehensive review Hogg postulates that there is still no definite proof that neutrophils are responsible for the capillary leak in ARDS.

Prostaglandins

Release of prostaglandins as a result of mechanical, chemical, bacterial and other insults, also leads to neutrophil and platelet aggregation, increased vascular permeability, systemic vasodilation, pulmonary vasoconstriction aand renovascular dilation (to compensate for sympathetic nerve-induced renal ischaemia).

The reversal or prevention of activation of the prostaglandin cascade by the use of non-steroidal anti-inflammatory drugs may contribute to the prevention of the development of ARDS in patients at risk, provided it is not administered to patients with incipient renal failure, in which case the reversal of its dilating effects on the kidney may lead to renal hypoperfusion.

Inappropriate Activation of Clotting Factors

Complement activation may also lead to the activation of the Hageman factor which is responsible not only for the activation of the intrinsic coagulation cascade and the fibrinolytic system, but also for the conversion of prekallikrein to kallikrein with the resultant formation of bradykinin. Dilution of blood can also activate prekallikrein.

The plasma kinins are potent vasodilator autacoids and in very low concentrations they cause arteriolar dilatation and increase capillary permeability producing oedema as well as other responses.

Lysis of phospholipid membranes release arachidonic acid which, when acted on by other enzymes (cyclo-oxygenase and lipoxygenase), forms leukotrienes and/or prostaglandins and thromboxane.

Activation of platelets in response to vascular endothelial damage leads to the release of thromboxane A2 which is synthesized by activated platelets and will increase ADP release and promote platelet aggregation. Platelet membrane phospholipid is made available on activated platelets which then serve as a congregating place for the coagulation proteins. Serotonin is also released by platelets. Activation of clotting factors play a role in the development of DIC and other thrombo-embolic phenomena which may precipitate or complicate ARDS. Serotonin and thromboxane A2 cause vasoconstriction. This vasoconstriction as well as blocking of small vessels by neutrophils, platelet aggregates and debris may be the cause of pulmonary hypertension and may lead to the formation of micro-thrombi.

Platelet-derived products have also been shown to induce pro-inflammatory changes. It has been shown that platelet activating factor (PAF) can accumulate in hypoxic tissues in a variety of pathological states including activation of platelets and release of thromboxane A2 as well as activation of neutrophils and increasing capillary permeability.

Once the release of vaso-active substances is set in motion a vicious circle starts with one system causing activation of another.

Beta Endorphin

Recently, release of another mediator has been implicated in the development of hypotension in patients with ARDS and endotoxic shock. The stress of various states of shock apparently provokes the release of beta endorphin from the pituitary. Beta endorphin binds to opiate receptors in the area adjacent to the medullary cardiorespiratory centres, causing depression of cardiovascular function.

This is the rationale for the use of the specific opiate antagonist, naloxone, in states of shock in an attempt to reverse the action of beta endorphin.

Surfactant Abnormalities

The effect of surface tension in causing collapse of an alveolus increases as the diameter of the alveolus decreases. The pressure generated in the air of the smaller alveolus will be greater than the pressure in the larger alveolus. Air is therefore displaced from the smaller into the larger alveolus. This continues until collapse of the smaller one occurs. This is referred to as instability of the alveoli. Surfactant prevents this from happening, stabilizing the size of the alveoli.

Surfactant is secreted by the alveolar epithelium into the fluids lining the alveoli. As the alveolus becomes smaller under normal conditions, surfactant becomes more concentrated and surface tension is reduced. In certain conditions (i.e. following extra corporeal perfusion of the lungs) surfactant secretion is impaired with an increased tendency for the alveoli to collapse. Surfactant requires an adequate blood supply for its production and ischaemic states would impair its production. Pulmonary oedema dilutes surfactant with a resultant increased tendency for alveoli to collapse.

Pathophysiology

Gas exchange takes place through the alveolar-capillary membrane, which has a thickness of 0.5 microns. The alveolar epithelium and the capillary epithelium rest on basement membranes. The interstitial space lies between the membranes and contains interstitial fluid, connective tissue and scattered fibroblasts. The membranes fuse at the capillary-alveolar interface. The capillary endothelial cells produce and degrade prostaglandins, metabolize vasoactive amines, convert angiotensin I to angiotensin II and produce, in part, factor VIII. The vasoactive agents may be partially responsible for regulation of ventilation and perfusion relationships. Membranous (type I) pneumocytes are highly differentiated and when damaged cannot replicate. The cells join one another tightly and are normally impermeable to water. Granular (type II) pneumocytes are more active metabolically. Type III pneumocytes resemble chemoreceptor cells.

The primary abnormality is diffuse leakage of proteinaceous fluid across the alveolar-capillary membrane, usually within 24 hours of the initial insult (exudative phase). Inflammatory cells and erythrocytes migrate into the interstitium and the alveoli. Type I cells are sensitive to this type of injury and are irreparably damaged, leaving a denuded basement membrane. Alveolar epithelial damage seems to be more prominent at this stage than endothelial damage. Oedema fluid collecting in the interstitial tissues is initially drained by the pulmonary lymphatics which is soon overwhelmed with fluid accumulating around terminal bronchioles and larger vessels. As the process continues, fluid accumulates in the interstitial space adjacent to the alveoli and subsequently collects in the alveoli. There is capillary congestion and the alveolar-capillary membrane is thickened.

There is simultaneous loss or alteration or dilution of surfactant which, coupled with obstruction of alveolar ducts and bronchioles, cause areas of collapse of terminal air spaces, where continued perfusion results in a veno-arterial shunt. In the early stages type II cells are fairly resistant to injury. Within approximately 72 hours, however, the type II cells start to proliferate bridging the denuded basement membrane - the early proliferative stage.

Aggregates of plasma proteins, fibrin, cellular debris and remnants of surfactant adhere to the denuded alveolar surface, forming hyaline membranes especially in the alveolar ducts and bronchioles. Over the next 3 to 10 days the alveolar septum is infiltrated by proliferating fibroblasts, palsma cells, leukocytes and histiocytes. Hyaline membranes organize and micro-atelectasis is seen (late proliferative stage). Even in initially extensively damaged lungs, fibrosis need not necessarily develop. However, fibrotic changes may develop by the end of the first week and often occurs first in alveolar septae and hyaline membranes. Microthrombi may be present. In hypovolaemic states the possibility of microthrombi forming is increased as a result of reduced flow in the small vessels. Since blood is composed of a suspension of particles (the erythrocytes) suspended in a colloidal solution, the plasma, it is a non-Newtonian fluid, that is, it has a viscosity which varies with the velocity gradient or shear-rate. Blood viscosity falls sharply with increasing shear-rate and *vice versa*. Its apparent viscosity also varies with the diameter of the tube along which flow is occurring. When blood flows along the bloodvessels at normal or increased flow rates, the suspended particles, the erythrocytes, tend to aggregate in the central stream leaving a layer of relatively cell-free fluid peripherally. The viscosity of the peripheral fluid is therefore less than the viscosity of the central stream resulting in a higher velocity gradient next to the vascular wall. As the blood flows into side branches leaving the main vessel, some plasma skimming occurs leading to blood with a lower haematocrit and therefore a lower viscosity flowing into progressively smaller vessels.

When hypovolaemia occurs, the flowrate decreases, axial streaming decreases and the erythrocytes, instead of aggregating in the central stream, are now suspended centrally as well as peripherally and this increased viscosity of blood flowing into the smaller vessels is partly responsible at least, for sludging, further slowing of blood flow and the formation of thrombi.

Fibrosis is most apparent in the respiratory ducts and bronchioles and may progress to widespread fibrosing alveolitis. Aspiration, oxygen toxicity, fluid overload and hypotension would exacerbate the whole picture.

At autopsy the lung is heavy (more than 1000 g) liverlike and oedematous, mostly due to the increase in extravascular lung water. The salient microscopic features of ARDS are interstitial and alveolar oedema, with extravasation of erythrocytes, fibrinous exudate of alveolar hyaline membranes as well as microthrombi. Fibrosis is seen in longstanding cases. There may be associated signs of multiple organ pathology, pulmonary barotrauma, DIC and thrombo-embolism.

Although ARDS is regarded as a diffuse inflammatory lung disease, the lung lesions are not homogeneously distributed through the lung parenchyma. In most patients the lesions are preferentially located in dependent regions of the lung.

Gravity probably plays a role in the development of nonhomgeneous densities in the lungs because it causes a higher capillary pressure and compression in the dependent portions of the lung. With ARDS due to aspiration the lesions are often denser in the right lung, not necessarily in the lower lobe.

Clinical Manifestations

ARDS develops in patients against a background of a primary pathological process which is associated with either hypoperfusion of the lungs or with direct trauma to the lungs, or is due to a lung injury as a result of noxious substances delivered to the lungs by the airways or the circulation.

Moore recognized four phases of progressive respiratory failure in association with trauma as far back as 1968. With some deviations a similar sequence of events occurs in ARDS whatever the primary aetiology.

In the first phase there is tachypnoea, hyperventilation, dyspnoea, tachycardia and sometimes a raised temperature. At this stage there is often no clinical or roentgenologic evidence of lung pathology.

During phase 2 there is relative physiological stability. Cardiac output is high and blood pressure is adequate. Urinary output is usually within normal limits depending on the adequacy of the original resuscitation. Hyperventilation with hypocapnia is present as well as hypoxaemia with a progressive increase in the venoarterial shunt fraction. The lungs are stiff. There are usually abnormal lung sounds (but not necessarily) and on roentgen films lung infiltrates can be seen. At this stage blood gases will show hypoxia often with a lowered pCO_2. In the third phase there is severe respiratory insufficiency with progressive worsening of the blood gases, lung compliance and lung infiltrates.

The fourth phase is characterized by gross venoarterial intrapulmonary shunts (in excess of 30% of the cardiac output), increased serum lactic acid levels, a progressive fall in pO_2 and rise in PCO_2 (metabolic as well as respiratory acidosis). There is usually associated pulmonary infection, often with relatively resistant organisms as well as multiple organ failure with disseminated intravascular coagulopathy, often as the final insult.

Intestinal ileus is often present early in hypoxic states. Trauma, surgery, severe sepsis and administration of nacrotics cause delayed gastric emptying. If not recognized, aspiration of intestinal contents might well deliver the *coup de grace* to an already severely compromized respiratory system.

Symptoms and Signs

With all patients, where the development of ARDS is a possibility, a high index of suspicion is necessary. Even small changes in the patients clinical signs must alert the nurse and the clinician to the possibility that a potential disastrous sequence of events is starting. In a London hospital the term, *1600 effect*, is used (MCCCM - minimal change capable of changing the clinician's mind).

The earliest sign is usually tachypnoea. This may be associated with dyspnoea and cyanosis. It is rather surprising how often the presence of cyanosis is missed even by experienced clinicians. The patient may have a cough and there is usually a steadily rising pulse rate. The temperature is often raised.

There is increased work of breathing, often associated with sweating and involvement of the accessory respiratory muscles. Changes in cerebration are common, progressing from normal cerebration through restlessness and confusion to lethargy and varying degrees of stupor.

Early in the development of the syndrome the lungs may be clear. As the pathology progresses, abnormal lung sounds develop - rales over parts of the lung or throughout all lung fields. Ronchi may be present.

Later in the course of the disease, symptoms and signs of sepsis and/or multiple organ failure develop, sometimes associated with the symptoms and signs of varying degrees of disseminated intravascular coagulopathy (DIC). Ileus and oliguria are common early findings.

Special Investigations

Serial blood gas analysis is essential in patients where there is suspicion of ARDS developing and where response to treatment must be monitored.

Hypoxaemia is the earliest clinical finding - often before definite symptoms and signs develop.

Chest x-rays may be clear early on or there may only be increased interstitial markings.

The interstitial infiltrates may progress to diffuse infiltrations which usually show areas of increased density in the perihillar areas or in the dependent portions of the lung. One lung may be more severely affected than the other.

In one recent case of near-drowning (fig. 3.9.i(a)) chest radiographs showed no abnormality approximately one hour after the incident, whereas films taken three hours later showed marked perihillar infiltrates. It may be difficult to differentiate from cardiogenic pulmonary oedema. However, there is usually an absence of pulmonary vascular redistribution, cardiomegaly or pleural effusion. Therapeutic measures (i.e. overhydration, positive pressure ventilation and infections) may alter the findings.

The infiltrates may gradually clear up or may change to a pattern of diffuse interstitial fibrosis or the oedema, the areas of atelectasis and consolidation, may become progressively worse, eventually showing diffuse lung consolidation or a "white-out" of the lung parenchyma.

Full blood count may show leukocytosis or leukopaenia. Some patients show a precipitous fall in total white blood cells at the onset of ARDS. Platelet count may be high, normal or low. Leukopaenia and a low platelet count should alert the clinician to the possible development of DIC. A rising leukocyte count may alert the clinician to the development of sepsis.

Leukopaenia in a patient with sepsis is a grave prognostic sign. The haemoglobin may be raised, (polycythaemia, dehydration or overtransfusion), normal or decreased. It often

shows a progressive decrease.

Analysis for clotting factors and fibrinogen defibrination products should be done to diagnose the development of DIC or other clotting disorders which may develop as a result of liver dysfunction or antibiotic administration.

Liver function tests may show signs of disturbed liver function as part of multi-organ failure and progressive worsening may be a bad prognostic sign.

An increase in the bilirubin value may be the only abnormal finding and may be an early sign of disseminated coagulopathy causing fragmentation of erythrocytes.

Haemolysis of transfused blood may also be responsible for elevation of bilirubin.

Serial cultures of bronchial secretions, wounds and urine, as well as blood cultures should be taken.

Positive findings have to be correlated with clinical findings in order to establish whether the positive culture is the result of infection, colonization or cotamination.

C-reactive protein determinations may show an increase, giving an indication of sepsis developing, often before there are other clinical signs of sepsis, such as a raised temperature.

Central venous pressure readings should be taken.

Insertion of a Swan-Ganz catheter should be considered if there is uncertainty whether the origin of the respiratory distress is cardiogenic or noncardiogenic or when there is uncertainty abouth the patient's state of hydration (overhydration or dehydration). It is possible, however, to treat critically ill patients without pulmonary flow catheters. A discussion of its benefits as well as the dangers of overuse and abuse is given by Robin.

Electrolyte (sodium, potassium, chloride, total CO_2, calcium, magnesium and phosphate) determinations should be done in order to adjust fluid therapy for optimum serum levels. Low serum phosphate levels are a common finding in patients on mechanical ventilation. Urea and creatinine levels are essential as well as creatinine clearance when indicated.

Peak and trough bloodlevels of drugs with a narrow safety margin should be done (i.e. aminoglycosides and digitalis).

Ultrasound studies, computerized tomography, magnetic resonance and other investigations may be required in the diagnosis of the primary disease or of complications.

Prevention of the Development of ARDS

The efficacy of measures to prevent ARDS from developing is almost impossible to assess, since not all patients at risk will develop ARDS.

Possible measures include:

- Early, adequate resuscitation of traumatized patients

- Early, adequate treatment of hypovolaemic shock, whatever the cause

- Early diagnosis and adequate conservative as well as surgical treatment of sepsis

- Early immobilization of fractures

- Optimum fluid balance (prevention of overhydration or dehydration)

- The lungs of patients with alveolar capillary leak are sensitive to excessive infusion of crystalloids

- Prevenetion of overtransfusion

- Prevention of haemolytic episodes. Injudicious warming of blood may cause haemolysis and denaturation of proteins which contribute to the development of microembolism and potentiates the activation of toxic plasma proteases.

In stored bank blood each of the major cascade systems in the plasma (complement, coagulation and kallikrein/kininogen) is partially activated. Activation of coagulation factors contribute to the development of ARDS as well as DIC. Activation of complement and kallikrein/kininogen release multiple proteases with vasoactive properties.

In incompatibility reactions the lysis of the red cells activates the coagulation system as well as the complement cascade.

- Nonsteroidal anti-inflammatory agents which suppress prostaglanding synthesis, may be of therapeutic value in the prevention of the development of ARDS in patients at risk, provided there is no incipient renal failure.

- Prevention of oxygen toxicity.

- Early recognition and adequate treatment of the ARDS.

- Early use of positive airway pressure ventilation may or may not be beneficial.

- Prevention of the development of hypoxia is essential.

Treatment

Patients with ARDS need meticulous care and even mild cases should be handled in an ICU.

The treatment of ARDS is threefold:

Specific treatment of the primary pathology is essential. Non-specific treatment should be aimed at keeping blood gases, haemodynamic status, fluid, electrolyte- and nutritional balance optimal. Prevention of complications may significantly improve the morbidity and mortality of ARDS.

Specific Treatment

This would depend on the primary disease. The very high mortality of ARDS in patients with sepsis is at least partly due to an infection resistant to treatment or to inadequately treated sepsis.

Non-Specific Treatment

There is still controversy about almost every aspect of the non-specific treatment or ARDS. Treatment should be adapted to the severity of the lung lesion and concomitant malfunction of other systems.

Ventilatory Support

Ventilatory support is necessary in most patients with clinical manifestations of ARDS.

Patients with mild ARDS with mild hypoxaemia can be managed without endotracheal intubation with CPAP.

Close monitoring is necessary especially as regards cerebration, exhaustion, respiratory and pulse rates and blood gases. If slowing of respiratory and pulse rates occurs, combined with sustained improvement of the bloodgases, the chances for complete clearance of the lungs without additional respiratory support is excellent. Unfortunately, in some patients the condition worsens and additional measures become imperative.

The classic criteria for the initiation of aggressive ventilatory support include a respiratory rate greater than 30-40 breaths per minute, a dead space/tidal volume ratio (VD/VT) greater than 0.6:1, hypercapnia, cyanosis and infiltrative changes on the chest x-ray and a PaO_2 of below 55.

These criteria ignore the importance of muscle fatigue in acute respiratory failure as a result of increased respiratory and cardiac work.

At rest oxygen utilization of the respiratory muscles accounts for approximately 2% of total body oxygen consumption. This value increases linearly with increasing ventilation. Ventilatory support may be required in some patients despite an adequately functioning lung

because of fatigue of the respiratory muscles. As ventilation increases an ever-greater proportion of the additional oxygen taken up will have to be diverted to the respiratory muscles at the expense of oxygen available for non-respiratory work, creating an oxygen steal syndrome. Apart from maintaining normal blood gases, the ventilatory apparatus plays a key role in maintenance of physiological acid-base status in the face of accumulating organic anions common to hypoperfusion states. In shock states an increase in ventilatory drive occurs unrelated to changes in acid-base balance, possibly due to stimulation of arterial or atrial baroreceptors.

The outcome of patients with ARDS might possibly be improved if aggressive measures to improve hypoxaemia is initiated earlier. Therefore, if the clinical signs (especially increased work of breathing, tachypnoea and tachycardia) and the hypoxaemia does not improve progressively on CPAP, or if the disease is discovered fairly late with tachypnoea, and increased work of breathing and hypoxaemia with hypocapnia or hypercapnia, intubation and positive pressure ventilation should be instituted.

Concomitant signs of disturbed cerebration should also be regarded as an indication for early intubation and positive pressure ventilation. Positive pressure ventilation (PPV) is a measure to keep the blood gases as near as possible to within normal limits. To achieve this, adjustments are made to minute volume (Vm), inspired oxygen concentration (FiO_2) and positive end-expiratory pressure (PEEP). To prevent oxygen toxicity the FiO_2 should, if possible, be kept below 50% and the rest of the variables adjusted to achieve normal levels of pO_2 and pCO_2. Pulmonary shunting was found to be least with an FiO_2 of 40%. However, normal blood gas values are not the only factor to be considered since the essential requirement is organ perfusion with oxygenated blood. Therefore adjustments should be directed to achieve optimal improvement of blood gas values with minimal circulation disturbance.

The optimum level of PEEP remains controversial with almost irreconcible differences of opinion.

Logically, the optimum level would be as advocated by Albert, namely, the lowest level of PEEP is used that maintains an adequate PaO_2 on an FiO_2 less than 50-60%.

Carroll concluded that PEEP should only be used to prevent hypoxaemia, employing the minimum level necessary to elevate the pO_2. In his series the mortality during shunt orientated PEEP was 27%. When PEEP was adjusted according to the PaO_2 levels the mortality was 4%. It is essential, however, not only to improve oxygen delivery but also to reduce oxygen requirements.

In patients with ARDS, oxygen consumption is raised. Increased respiratory work and fever, as well as sepsis also increase oxygen consumption. Restlessness and agitation increase oxygen requirements. Metabolic rate falls about 6% per degree centigrade fall in temperature.

Tissue oxygen supply and oxygen transport are impaired by hypoxaemia as well as by hypoperfusion states. Tissue oxygen uptake is therefore defective being almost linearly dependent on oxygen delivery (supply dependency). Therefore, apart from improving oxygen delivery, oxygen balance can be improved by reducing oxygen consumption.

Muscle relaxation and sedation reduce oxygen consumption. Gilston mentions striking improvements in patients with florid ARDS by using a combination of PPV, sedation, muscle relaxation and mild hypothermia. The following is a summarized general guideline for the sedation of patients on a ventilator where the goal usually is to achieve a reasonably aware, comfortable and quiet patient who does not fight the ventilator.

- A variety of analgesics and sedatives can be used.

- Good coordination with the ventilator can be achieved in the majority of patients with a continuous infusion of fentanyl. It is primarily a μ agonist, has respiratory depressant effects and produces analgesia and euphoria. Cardiovascular dynamics are not altered significantly when fentanyl is administered in a continuous infusion. Fentanyl also lowes metabolic requirements and energy expenditure and its effects on gastric motility are less than that of morphine.

- If additional sedation is required, an IV benzodiazepine such as midazolam, lorazepam or flunitrazepam can be administered. In patients with a persistent tachycardia and a labile circulation, hydroxyzine may provide sufficient additional sedation.

- In most patients muscle relaxants are only added to the analgesic-sedative regimen if additional muscle relaxation is required.

Normothermia

If the patient is hyperpyrexial, specific treatment is directed to control the cause of the pyrexia and nonspecific treatment is directed to keeping the temperature within normal limits.

Infection Control

Antimicrobial Coverage

The development of infection continues to be a major problem. Patients suffering from failure of vital organ systems have impaired defence mechanisms against infection. The use of invasive techniques for monitoring and support, further increases the risk of infection. The infection rate is directly connected to the duration of treatment. After one week of intensive care the infection rate increases to over 80%.

Endogenous infections are caused by potentially pathogenic micro-organisms (PPM) from the patients own microflora, whereas exogenous infections are caused by PPM from outside the patient. Although the causative PPM are exogenous these infections are called "secondary endogenous" because the multiplication phase in the oropharynx or intestines is essential in the pathogenesis. In "primary endogenous" infections the patient has already been colonized by the causative PMM on admission.

In general, infection prevention is based on two principles:

- The prevention of transmission of PPM by handwashing, barrier nursing and disinfection procedures which reduce the incidence of exogenous infections.

- The prevention of the emergency of bacterial resistance by a restrictive antibiotic policy.

This entails only short perioperative antibiotic prophylaxis, not treating colonization and specific antibiotic therapy only on clinical evidence of infection. However, in the severely ill patient it is almost impossible to distinguish between colonization and infection and if a full-blown infection is allowed to develop in a critically ill patient, the chances are that antibiotic therapy will be ineffective.

Bacterial infection is closely linked to both over-all survival and the occurrence of multi-organ failure. Bacterial pneumonia occurs in most patients with established ARDS and can be a sufficient cause of multi-organ failure even in the absence of other sites of infection. Parenteral antimicrobial therapy does not rapidly eliminate gram negative bacilli from the lungs once pneumonia has been established, although treatment at an earlier stage (shortly after inoculation) with the organisms, may do so.

Ileus encourages the growth of colonic flora in the stomach and the small intestine. Alkalinizing drugs encourage colonization of the stomach by micro-organisms which may then be a source of infection of the respiratory tract. It is therefore imperative that the pH of the gastric contents remain low. Most drugs used to prevent the formation of stress ulceration would therefore predispose to colonization of the stomach.

The use of selective suppression of the oral and intestinal flora with topical nonabsorbable antibiotics have been proposed by Stouenbeen, van Saene and Zandstra. Their aim is to eliminate aerobic PPM from the microflora. The antibiotics used in selective suppression should have low minimal bactericidal concentrations, be nonabsorbable and not be inactivated by food or faeces. They combined polymyxin E, tobramycin and amphotericin B and administered it four times daily in the oral cavity and into the gastrointestinal tract.

Systemic prophylaxis is essential in patients with ARDS since more than 50% of ARDS patients develop pneumonia. Soutenbeek, van Saene and Zandstra currently advocatge the use of cefotaxime as a suitable antibiotic for systemic prophylaxis. It has few side effects, a broad therapeutic range, with little effect on the indigenous flora.

Pneumocystis carinii may complicate ARDS in immuno-compromised patients and if suspected or diagnosed (lung biopsy), should be treated with cotrimoxazole (trimethoprim-sulfomethoxazole).

Whatever clinician's antibiotic regimen it should be adjusted according to the individual patient's needs, to the resistance pattern of micro-organisms in that particular hospital, to the primary disease, to the development of superimposed infections and to the results of serial cultures and sensitivity tests on blood, bronchial secretions, wounds and urine.

Immunoglobulins may be of value as supportive therapy in immuno-compromised patients.

Antiserum to neutralize endotoxin may prevent some of the deleterious effects of endotoxaemia.

Maintenance of Circulation and Fluid Electrolyte Balance

Haemodynamic management depends on improving the two components of oxygen transport - arterial oxygen content and cardiac output.

Positive pressure ventilation improves arterial oxygen content, but causes decreased venous return and a drop in cardiac output.

Sedation and analgesia is often required for intubation and maintenance of the patient on a ventilator. In a patient with a labile circulation or hypovolaemia this may precipitate a disastrous fall in cardiac output.

To counteract the adverse haemodynamic effects, increasing the preload with a fluid challenge may be sufficient, especially if colloid (albumin) is added. However, it may be necessary to infuse inotropic agents to maintain cardiac output. Dopamine increases the pulmonary shunt function, but PEEP eliminates this effect.

If infusion of crystalloids, albumin and inotropic agents are ineffective, an infusion of Dextran 40 sometimes improves perfusion quite dramatically.

Although overhydration can exacerbate the pulmonary oedema, great care must be taken to prevent dehydration. As a result of the widespread capillary leak there may be a combination of intravascular hypovolaemia and interstitial oedema. The intravascular hypovolaemia may be responsible for hypoperfusion of vital organs (myocardium, lungs, kidneys, brain and gut) and may be a contributing factor in the development of multiple organ failure. Hypoperfusion of the intestines may lead to increased permeability which may contribute to intestinal micro-organisms being absorbed into the bloodstream.

///leakage in the lung and sufficient fluid for adequate tissue perfusion. Patients presenting with ARDS may be in a state of normal hydration or may be in a negative or positive fluid balance. The volume of fluid infused should therefore be adjusted accordingly.

If the patient is clinically in a normal state of hydration with normal blood pressure, adequate peripheral perfusion, a urinary volume above 1 mL/kg/h, as well as normal serum urea and creatinine levels, the volume of crystalloid solution infused should be carefully adjusted so as to maintain a slight to moderate negative balance.

If the patient is in a negative fluid balance (with signs of dehydration, poor peripheral perfusion, lowered blood pressure, oliguria, high urinary SG, increased serum urea level, low CVP and pulmonary wedge pressures), initial fluid loading is necessary to correct the deficit, followed by maintenance of a mild controlled negative balance.

If the patient is overhudrated controlled fluid restriction and diuretic therapy is combined to correct the overload.

The type of crystalloid infused depends on the serum electrolyte (sodium, potassium, chloride, total CO_2, magnesium, calcium and phosphate) values and should be corrected to within normal limits.

In low perfusion states crystalloid solutions may prove insufficient to correct the condition.

Even where increased capillary permability is part of the pathological state, resuscitation with colloids has been more efficient, and caused less pulmonary and peripheral oedema. Colloid leakage into the interstitial space is variable, but 3/4 if not more of crystalloid solution will leak into the interstitial space. Crystalloids will cause a greater expansion of the interstitial space and should be used as such and a colloid solution (preferably albumin) should be used for expansion of the vascular space. The rational course to pursue therefore would be to infuse crystalloid as well as colloid solutions.

If the patient's serum albumin is below normal levels, albumin is infused to correct the deficit. Arguments against administration of albumin have been the leakage of proteinaceous fluid /// not and marked hypoalbuminaemia will contribute to the development of pulmonary as well as peripheral oedema.

The argument against the infusion of a large volume additional crystalloid solution for the purpose of improving peripheral circulation is that it will lower the colloid oncotic pressure leading to an increase in pulmonary oedema formation.

An optimum haemoglobin level is important for oxygen and CO_2 transport and attention should therefore be given to the correction of anaemia which may develop in the absence of active bleeding. However, overenthusiastic blood transfusions may lead to worsening of the lung infiltrates and deterioration in the patient's condition.

With very severe pulmonary involvement it may be wise to withold correction of a lowered haemoglobin until progressive clearance of the infiltrates takes place, provided the haemoglobin level does not drop below a haematocrit of 27 (also provided that no active bleeding is taking place). Once definite improvement is established gradual correction of the haemoglobin is undertaken.

Maintenance of Kidney Function

The maintenance of kidney function is closely related to fluid balance. Renal function is often compromised early in the development of ARDS especially if the primary disease is or has been associated with hypovolaemic or septic shock. Restoration of adequate intravascular volume is therefore the first step in the maintenance of adequate kidney function. On the other hand certain therapeutic measures tend to contribute to retention of fluid (positive pressure ventilation, parenteral nutrition).

Meticulous examination, intake and output calculations as well as serum electrolyte, urea, creatinine and omsolarity estimations with, when indicated, CVP and pulmonary wedge pressures are necessary to evaluate the patient's fluid and electrolyte requirements.

Where there is evidence of overload or fluid ///. This is often /// if the patient is oliguric. Therapy with diuretics is then indicated. Instead of repeated doses of a diuretic, good results have been achieved with a combination of mannitol, furosemide and aminophyllin (if there is no contraindication to the administration of aminophyllin) via a continuous infusion.

The dose of fureosemide in the combination and the rate of the infusion is adjusted for the production of a controlled volume of urine with adjustments in the volume of fluid replaced (50-80% of fluid lost) to achieve a slightly negative fluid balance.

It is preferable to achieve a controlled negative balance with high intake and output volumes. Restricted fluid intake in a severely ill patient with oliguria with occasional spurts of diuretic-induced polyuria can develop oliguric renal failure within hours even in the presence of overhydration.

Diuretics should not be administered to oliguric patients with hypovolaemia as they may further decrease blood volume and cause acute tubular necrosis.

In patients with oliguria, especially if associated with a low perfusion state, infusion of low-dose dopamine in order to improve renal blood flow, can be utilised to induce a diuresis.

In patients with incipient renal failure, nephrotoxic drugs should be avoided, if possible. If it has to be administered the dose of the drug should be adjusted and blood levels controlled.

Inhibitors of prostaglandins should also be avoided in patients with incipient renal failure.

Corticosteroids: To Give or Not To Give?

The rationale for the administration of corticosteroids in the ARDS is the ability of cortisol and its analogues to suppress inflammatory reactions. At the microscopic level there is inhibition of oedema formation, fibrin deposition, capillary dilatation and complement-induced migration of leukocytes into the inflamed area in the early stages of the inflammatory process. They also inhibit later manifestations such as capillary proliferation, deposition of collagen and cicatrization.

In clinical terms, the administration of corticosteroids for their anti-inflammatory effects is /// necessary. The underlying cause of the disease remains. It is this suppression of inflammatory responses that has made the corticosteroids valuable therapeutic agents. It is also this property that gives corticosteroids its singular potential for therapeutic abuse and mishaps. Most of the complications of corticosteroid therapy occur with prolonged therapy.

The development of delayed wound healing, adrenal insufficiency and peptic ulceration (with its high incidence of perforation or haemorrhage in the presence of cortisone therapy) is unlikely with short-term corticosteroid administration.

The main disadvantage of corticosteroid therapy in the patient with ARDS is the increased susceptibility of the patient to infection and delayed healing.

Hyperglycaemia, if it develops, can be controlled with insulin.

There have been reports of myocardial ischaemia with rapid injection of a large dose

of methyl-prednisolone succinate (MPN) - probably due to anaphylaxis.

There is still controversy whether cortisone therapy improves survival in patients with ARDS or not. Amongst others, Gates, Huang and Cheney performed studies with acid aspiration in dogs and could demonstrate no beneficial effects.

According to Shumer steroid therapy can prevent the injury to the lung provided it is administered before the primary insult or shortly afterwards.

Kalter *et al* reported favourable effects on haemodynamics and oxygenation with methylprednisolone (MPN) therapy in patients with septicaemic shock. (MPN was administered as a single dose of 30 mg/kg IV immediately after initial volume loading). An increase in lactate concentration was observed, but since haemodynamic improved, they postulated that it possibly reflected a "wash-out" of lactate from the tissues.

Studies done by Hartvig-Jensen and Anderson showed a reduction of mortality in patients with septicaemia provided MPN is given before the development of circulatory shock. Mention is not made on the presence or absence of ARDS in these patients.

In a series of 99 patients with ARDS it was found that there was no difference in mortality or reversal of RDS or development of complications in the patients treated with MPN and the patients not treated with MPN.

In a multicentre trial involving 304 patients with sepsis and ARDS the results showed an increased incidence of ARDS in the MPN-treated group, (32% versus 25% in the placebo group), 31% reversed their ARDS in the MPN-treated group compared to 61% in the placebo group. The 14 day mortality was 52% in the MPN-treated group compared to the placebo group's 22% and there was significantly increased incidence of mortality directly attributed to secondary infection in the MPN-treated group.

The dose regimen varies, but is usually in the megadose category - 30 mg/kg as a single dose, or as two or three 8-hourly doses or 30 mg/kg given in divided doses over 24-48 hours.

Although earlier reports on corticosteroid therapy for the prevention and treatment of the ARDS was promising, later reports showed either no effect on the course of the illness or an increase in morbidity and mortality. The current trend of thought therefore seems to be that corticosteroid therapy actually compromises the outcome of the ARDS and that it should not be administered.

Beta blockade has been suggested to protect the lung against the effects of prolonged increased catecholamine release which occurs in patients with raised intracranial pressure.

20% of patients with head injuries as the only trauma develop respiratory failure.

Elevation of intracranial pressure causes increased release of catecholamines setting in motion a process leading to pulmonary oedema. In experimental studies in dogs, there were indications that beta blockade (propranolol) can protect the lung against the effects of

excessive sympathetic stimulation.

Maintenance of Nutrition

Maintenance of nutrition is essential. Initially total parenteral nutrition (TPN) is necessary since the majority of the patients will have an ileus. TPN should be started early. It has been found that patients develop oliguria rapidly if TPN is started while the patient is still hypovolaemic especially if the urea levels are raised. Therefore, one should attempt to normalise bloodvolume and correct electrolyte disturbances and hypo-albuminaemia before instituting TPN. In patients with existing hypo-albuminaemia, TPN is unlikely to raise the albumin level to normal. The regimen should include trace elements and vitamins (water as well as lipid soluble).

As soon as the patient starts to absorb from the bowel, nasogastric feeds should be resumed. Absence of bowel sounds during mechanical ventilation is not necessarily a sign of absence of bowel movement. Periodic trial administration of fluid and subsequent aspiration should be done to test absorption.

Prevention of Stress Ulceration

High gastric-acid related stress ulceration of the gastrointestinal tract is a common complication in the severely ill patient. Certain drugs such as corticosteroids and prostaglandin inhibitors contribute to the development of erosions of the gastric or duodenal mucosa.

In an attempt to reduce the incidence of stress ulceration the logical course seemed to be the alkalinisation of the gastric contents by administering H2 antagonists (cimetidine or ranitidine) or antacids.

The incidence of stress ulceration dropped, but colonization of the stomach by often resistan strains of bacteriae and fungi, occurred. This increased the incidence of nosocomial infections of the respiratory tract.

Possibly the safest substance for the protection of the gastric mucosa at this stage, is sucralfate. It is a complex substance formed from a sulfated disaccharide (sucrose) and polyaluminium hydroxide. It is available as a tablet or a suspension. It forms a gel that adheres strongly to epithelial cells and to the base of erosions or ulcer craters. The gel prevents the exudation of proteins from erosisons and also absorbs pepsin, trypsin and acids. The gel does not neutralize the gastric HCl so that the gastric contents retain its low pH and its ability to prevent bacterial colonization of the stomach.

In a series of 100 patients receiving either an antacid or sucralfate the incidence opf pneumonia was 10% with sucralfate versus 34% with the antacid.

In another series ofd 130 patients on mechanical ventilation, given antacids and/or H_2 blockers, or sucralfate via a nasogastric tube, the mortality rate in the antacid/H_2 blocker group was 1.6 greater than the sucralfate group, whilst the incidence of pneumonia was twice as high and the growth of gram negativce bacteria in the stomach was also higher.

Extra-Corporeal Membrane Oxygenation (ECMO)

Patients with severe ARDS were treated with ECMO but it is still uncertain whether ECMO will contribute to the survival of patients with ARDS. A modified version of ECMO utilizing ECMO only for the reduction of CO_2 (EC CO_2 R) has been tried but it is still largely experimental.

Gotloib and Barzilay described a technique utilizing haemofiltration for ARDS.

Complications of ARDS

Most nonsurvivors with the ARDS, die from the pre-existing condition or as a result of sepsis often leading to multi-organ failure and DIC. If mortality is to be reduced, attention should be focused towards prevention of sepsis and subsequent multiple organ failure. During the course of treatment for severe ARDS, the possibility of a sequence of complications developing increases with the length of treatment.

Infection

Bacterial, Viral, Fungal

Sinusitis, stomatitis (often monilial after prolonged antibiotic treatment), laryngotracheitis, nosocomial pneumonia, septicaemia, pyelitis, cystitis, vaginitis.

Aspiration

Aspiration of gastric contents before intubation or past the endotracheal or tracheostomy tube.

Thromboembolism

- Pulmonary emboli (micro and macro)

- Deep vein thrombosis

- Thrombo-phlebitis due to IV infusions

- Arterial thrombi or emboli due to arterial cannulae with ischaemia distal to the thrombosis

- DIC (varying degrees)

Vital Organ Failure

- Renal failure

- Hepatic failure

- Cardiac arrhythmias, cardiovascular collapse

- GIT (gastric atony, ileus)

- CNS - depressed cerebration, localised neurological lesions

Haemorrhagic

- DIC

- Abnormality of clotting factors (thrombocytopaenia, lowered prothrombin)

- Gastro-intestinal haemorrhage

- Nasal or tracheal haemorrhage

Fluid and Electrolyte Disturbances

Dehydration, overhydration, fluid retention, electrolyte abnormalities.

Malnutrition

This is often associated with hypoproteinaemia and anaemia.

Barotrauma

Pulmonary interstitial emphysema, subcutaneous emphysema, pneumothorax, pneumopericardium, pneumoperitoneum

Complications of Endotracheal Intubation, Tracheostomy

- Bleeding from the nose or trachea

- Mechanical obstruction of tube

- Accidental extubation

- Inability to seal the airways

- One-lung intubation

- Sinusitis

- Laryngotracheitis

- Arytenoid ulceration

- Nosocomial pulmonary infections

- Tracheal stenosis (incidence higher with tracheostomy than with ET intubation)

- Oesophagotracheal fistula

Ventilator Malfunction

Pulmonary Atelectasis

Bronchopulmonary Dysplasia

Neurological Complications

These include confusional states, obtunded cerebration, localised disturbances of function (temporary paralysis of central origin - unknown aetiology).

Two patients with severe ARDS who developed blindness, were encountered - in one case it was permanent with bilateral optic atrophy, in the second patient the blindness was cortical and cleared up. Another patient developed a temporary quadriplegia and two others temporary hemiparesis. Peripheral nerve lesions can occur, usually as a result of localised pressure.

Polyneuritis can occur in critically ill patients.

Pressure Necrosis

Psychiatric Disturbances

Phlebitis (Infusion Related)

Complications as a Result of Invasive Monitoring Techniques

Pulmonary Artery Catheter

- Localized infection

- Septicaemia

- Right-sided endocardial infection

- Localised haematoma

- Internal jugular stenosis

- Internal jugular thrombosis

- Pulmonary artery thrombosis or embolism

- Pulmonary artery rupture

- Pulmonary haemorrhage

- Right atrial thrombosis

- Cardiac dysrhythmias

- Right-sided endocardial lesions

- Mechanical obstruction of the catheter

- Balloon rupture

- Air embolism

- Pneumothorax

In a study of 70 critically ill patients 4% died as a result of Swan-Ganz catheter related complications and 20-33% had major complications requiring treatment.

Intra-Arterial Cannulation

Radial Artery

- Thrombosis with ischaemia of the hand or fingers

- Localised infection

- Infection, with septic emboli. Localised formation of Osler's nodes resulting from septic emboli has been reported

Septicaemia

- Cerebral embolization (with vigorous flushing)

- Haematoma

- Aneurysm-formation at the puncture site

Percutaneous axillary or femoral artery cannulation has been recommended for long-term cannulation, possibly with fewer complications.

The infection rate for intravascular catheters varies from 3.8-57%. There is correlation between the incidence of colonization and technique and conditions of insertion; contamination of infusion fluid, tubings and dressings; and foci of infection with spread to the cannula via the bloodstream.

Colonization was decreased by changing the dressings once daily.

Meticulous nursing and medical care are essential if complications are to be avoided. Repeated clinical examinations as well as serial special investigations should be carried out to alert the clinician as early as possible to the development of complications. Active measures should also be taken in order to prevent any of them from occurring.

Monitoring should be adjusted, depending on the severity of the pathology and the facilities available.

Observation

Neurological status:

- Level of consciousness (mental state)

- Localising neurological signs

- Seizures

Skin and mucosa:

- Colour

- Humidity

- Texture

- Temperature

- Pressure points

Ventilation:

- Colour

- Respiratory rate, rhythm, depth, chest movement, accessory respiratory muscle movement

- Lung sounds

If on PPV

- ventilator settings

- coordination with ventilator

Cardiovascular

- Pulse rate, volume and rhythm

- Congestion of neck veins

- Blood pressure

- Peripheral pulses

- Signs of deep vein thrombosis

- Heart examination

Temperature

Signs of oedema

Abdomen:

- Distention

- Tension in abdominal muscles

- Tenderness

- Palpable enlargement of liver, spleen

- Bowel sounds

- Volume of losses from GIT

- Presence of blood in aspirate

Bladder:

- Incontinence

- Retention

- Overflow retention

- Catheter

Urine:

- Volume and SG (hourly) (correlate with intake)

- Fluid and food intake (correlate with losses)

- Weight

Continuous ECG

Chest X-Rays

- Serial

Noninvasive Impedance Cardiac Output Monitor

Laboratory Tests

- Sodium, potassium, chloride, total CO_2, calcium, magnesium

- Phosphate, glucose

- Urea and creatinine

- Total proteins and albumin

- Full blood count

- Blood cultures

- Cultures of bronchial secretions, wounds and urine

- Liver function

- Defibrination products and clotting factors

- Tests for, i.e. malaria, rickettsial disease, HIV, etc.

Invasive Monitoring

- Arterial pressure

- Central venous pressure

- Pulmonary artery pressures

With the availability of diverse and sophisticated monitoring equipment it becomes all too easy to lose sight of the patient as an entity. It is therefore imperative to correlate the results of special investigations with the patient's clinical status.

The degree of sophistication of the monitoring techniques depends not only on the severity of the disease but also on the sophistication of the nursing care. One should be careful not to fall into the trap of, what Leonard Peikoff calls, albeit in a philosophical sense, "complexity-worship".

Measurements and monitoring have intrinsic risks as well as benefits. Some of the

risks are as follows:

- Technical errors may invalidate the results or lead to incorrect decisions

- Misinterpretation may lead to bad decisions

- Injuries due to invasive techniques

- Information overload may distort priority selection.

Prognosis

The mortality rate of the ARDS remains in the region of 60% and close to 100% when it is associated with severe sepsis. In one series the overall mortality of the ARDS, which included patients with hematologic/oncologic problems, was 82%. When those patients were excluded the survival rate was 50%.

Factors that correlate with prognosis are: age, systolic blood pressure on admission, preadmission functional status, severity of the primary disease, treatment available, response to treatment, sepsis and multiple organ failure and development of DIC.

The presence of intravenous and intra-arterial cannulas, urinary catheters, endotracheal tubes, the use of ventilators, administration of, for instance, immuno-suppressant drugs, corticosteroids, nephrotoxic drugs, hepatotoxic drugs, antibiotics, H2 antagonists, increase the possibility of the development of complications and drug reactions enormously.

Inadequate surgical drainage of abscesses, failure to diagnose a gangrenous gallbladder or gangrenous bowel or leakage from the intestines at an early stage is at least partly responsible for the poor prognosis of the ARDS.

Poor choice of antibiotics or an inadequate dose regimen will contribute to the emergence of resistant strains of bacteriae. Another indication of a poor prognosis is poor patient response (failure to develop fever at the onset of an infection, leukopaenia, low platelet count).

Failure to correct fluid and electrolyte imbalance and hypo-albuminaemia will also compromise recovery. Malnutrition will predispose to the development of infections and will be responsible for muscle weakness with resultant problems in weaning the patient from the ventilator, leading to prolonged time on the ventilator with the increased possibility of complications such as infection and thromboembolism developing.

Risk factors for the development of ARDS have already been enumerated. These factors are additive. Incidence of ARDS with one risk factor was reported as 25%, with two risk factors as 42% and with three as 85%.

In order to evaluate the outcome from a severe acute illness such as ARDS, an assessment model can be used to estimate the pretreatment risk of death. The APACHE (acurte physiology and chronic health evaluation) and its revision APACHE II uses

information from the patients initial physiologic abnormalities to measure acute severity of disease and combine this with points awarded for the increased risk of death associated with pre-existing health problems and age, to produce a total score which varies from 0-50 and provides a cardinal index number to evaluate prognosis.

Comment

A. van Eaden

A clear distinction must be made between **respiratory** support and **ventilatory** support. One could see respiration as consisting of two different entities - oxygenation and ventilation. The former can be improved with oxygen and/or PEEP and the latter by ventilation and/or PEEP.

The Main Indications for Respiratory Support

- Increased $AaDO_2$ - a low PaO_2 for the given FiO_2. Support in this instance means administration of oxygen and/or PEEP and not necessarily mechanical ventilation. A PaO_2 of 60 mm Hg, haemoglobin saturation of 90%, is usually adequate.

- Increased $PaCO_2$ or respiratory acidosis. Treatment now implies mechanical ventilation or, less frequently, extracorporeal removal of CO_2. Use the minimum frequency that will keep the pH above 7.3 and the pCO_2 at an acceptable level.

- Increased work of breathing. This should be treated with a ventilator, which takes over the work of breathing or with PEEP/CPAP which decreases the work of breathing by changing the compliance of the lungs. PEEP seems to offer a distinct advantage in that it improves oxygenation and reduces the work of breathing. The mechanism of the latter will be considered.

PEEP will probably has little effect on $PaCO_2$ and because hypercapnea is not often a problem in ARDS the use of CPAP is often all that is needed for respiratory support, even in severe ARDS.

The mechanism by which PEEP changes the elastic work of breathing:

Work = Force x Distance = Intrapleural pressure change x tidal volume (VT)
= △P△VT

Compliance = △Volume / △Pressure

Thus elastic work per breath = 1/2 V2/T / C

Work per minute = (1/2 V2/T / CT) x f

ARDS causes a decrease in compliance and thus an increase in the work of breathing. Because work increases directly proportional to the square of the tidal volume the patient will respond by decreasing the tidal volume. To prevent CO_2 build-up the respiratory rate

increases. This is economically advantageous, but it still means increased work of breathing. The patient now takes rapid shallow breaths and to some extent uses the accessory muscles of respiration.

As the FRC decreases, the triangular area that represents the work of breathing (see fig. 3.9.1b) shifts to a less economical point on the compliance curve and the work of breathing increases. The compliance curve itself shifts to the right. The administration of PEEP may increase the FRC and shift the triangle to a more favourable position on the slope of the compliance curve (see figure 3.9.2) and so decrease the work of breathing. This work may be nearly normalized by the judicious use of CPAP and this should be the first line of treatment in the **respiratory** support of ARDS.

If CPAP support does not decrease the work of breathing sufficiently as reflected by a decrease in the respiratory rate, pulse rate, respiratory effort and blood gases, ventilatory support should be given. The minimum IMV rate should be used which will keep the pH > 7.3 or the pCO_2 at an acceptable level. Hyperventilation should be avoided at all times except if indicated for concommitant cerebral pathology.

When the patient inhales, the pressure to the right of the unidirectional valve drops below atmospheric pressure, the valve opens, and the patient is allowed to take in a tidal volume. Should PEEP of about 10 cm H_2O be applied to the expiratory valve the unidirectional valve will remain closed till the pressure to the right o fthe valve again drops to subatmospheric levels. Only then will the valve open to allow gases to flow through and enable the patient to take in his tidal volume. To initiate this drop of 10 cm H_2O requires work and this work of breathing is caused by the system.

If a reservoir bag is fitted over the opening opposite the fresh gas flow inlet a pressure of about 9 cm H_2O on the left-hand side of the unidirectional valve can easily be obtained. An inspiratory effort of slightly more than 1 cm H_2O will drop the pressure on the right-hand side of the valve (10 cm H_2O) enough to allow the valve to open and the patient to breath. The extra workload of breathing caused by PEEP can be diminished in such a system by building up pressure to the left of the valve to a value just less than the PEEP by high fresh gas flows.

If a patient breaths from the system illustrated in fig. 3.9.3, the following changes inj airway and intrapleural pressures takes place. Without PEEP the airway pressure drops a little to open the valve and to allow inspiration. The intrapleural pressure changes from - 2 cm H_2O to - 7 cm H_2O to establish a tidal volume exchange. Assuming a VT of 500 mL and lung compliance of 0.1 L/cm H_2O. When PEEP (i.e. 10 cm H_2O) is applied to the expiratory airway, pressure rises 10 cm H_2O and assuming 50% of airway pressure is transmitted, the intrapleural pressure rises to + 3 cm H_2O. If the system does not allow for pressure buildup to the left of the unidirectional valve, the airway pressure will have to drop to subambient as shown in fig. 3.9.4 before the valve will open to allow gas flow. For the airway pressure to drop by 10 cm H_2O, the intrapleural pressure has to drop by at least 10 cm H_2O. (Ignoring compliance in the tubes of the respiratory system).

This intrapleural pressure drop of 10 cm H_2O is needed just to overcome the effect of PEEP on opening of the valve. The intrapleural pressure will still have to be lowered a further

5 cm H_2O to establish a tidal volume exchange again assuming VT of 500 mL and lung compliance of 0.1 L/cm H_2O. Note that though PEEP is used, this is not CPAP because the inspiratory pressure is not positive (above atmospheric pressure).

When using a bag to allow pressure build up to the left of the unidirectional valve, to a value just less than PEEP, the intrapleural pressure has to be lowered only a little before the valve opens and the inspiratory airway pressure remains positive (CPAP). The nearer the IPAP (inspiratory positive airway pressure) to the EPAP (expiratory positive airway pressure which is another name for PEEP) the less the work of breathing needed to overcome the extra work created by the respiratory support system.

A demand valve triggered by a negative pressure of 0.5-1.0 cm H_2O works well and is used in ventilators. Some ventilators do not respond well when PEEP is applied and at least one on the market signals increased respiratory rates if sensitivity is set at -0.5 cm H_2O. This triggers the alarms forcing the nursing staff to change the sensitivity to -3 cm H_2O or more, causing an increase in the work of the breathing for the patient. A very unsatisfactory situation.

Fig. 3.9.2 shows that the mean intrapleural pressure changes when PEEP alone are not higher than with normal breathing and consequently has little effect on venous return and cardiac output, but with an unacceptable increase in the work of breathing. CPAP too does not decrease venous return significantly but has little adverse effect on the work of breathing.

Although controlled mechanical ventilation takes over the work of breathing completely, it tends to interfere with venous return by increasing the mean intrapleural pressure.

Chapter 3.10: Haemostasis

R. C. Franz

Haemostasis encompasses all the physiological processes which act in concert to prevent or arrest bleeding from a blood vessel. The process which is brought about by extravascular, vascular or intravascular mechanisms results in haemostasis. An exaggerated response produces thrombosis. Clot dissolution or fibrinolysis, although not a component of the haemostatic mechanism, may be a cause of excessive bleeding.

Extravascular Mechanisms

These are related to the pressure exerted by the elasticity of the tissues which surround the injured vessel. The bleeding tendency associated with conditions when there is a mesenchymal defect (i.e., cutis laxa, Ehlers Danlos syndrome) relates inter alia to inadequate elasticity of the supporting tissue at the site of vessel injury. The compressive effect of intramuscular haematoma tends to occlude the venules and capillaries where a low pressure system prevails. Conversely a ruptured artery in the floor of a peptic ulcer often continues to bleed. Similarly the decompressive effect following an abdominal incision for a ruptured liver may lead to rapid exsanguination if not controlled by the insertion of abdominal packs.

Vascular Mechanisms

Constriction of the injured vessel is brought about by contraction or spasm or the smooth muscle fibres. It has also been shown that opposition and adhesion of damaged endothelial cells may be sufficient to obliterate microdefects. Although the release of vasoactive amines and thromboxane A_2 from activated platelets may contribute to vasospasm, these agents do not appear to be a prerequisite for the vascular response.

Intravascular Mechanisms

Primary haemostasis involves constriction of the injured vessel, exposure of subendothelial collagen and the adhesion and aggregation of activated platelets on the damaged intimal surface to form the primary haemostatic plug. This process also involves the participation of von Willebrand factor, a plasma glycoprotein which mediates platelet adhesion and the platelet release of vasoactive agents that augment aggregation. The platelet plug formed is associated with the release of serotonin and adenosine diphosphate which are responsible for further platelet aggregation. The subsequent release of prostaglandin endoperoxides (PGA2 and PGH2) and thromboxane A2 (TXA2) stimulates aggregation, viscous metamorphosis and the release of several procoagulant platelet factors. TXA2 is a potent vasoconstrictor.

Platelets play a cardinal role in the initiation, persuance and successful completion of the coagulation process. The release of platelet factor 3 (phospholipid) provides the fundamental cofactor in the coagulation cascade. Platelet factor 3 is required for the activation of factor X as well as for the reaction by which activated factor X (Xa), factor V and calcium activate prothrombin to thrombin (platelet factor 1, which relates to coagulation factor V in platelets, and platelet factor 2, which accelerates the clotting of fibrinogen by thrombin, are terms which are no longer used). Platelet factor 4 is a potent antithrombin which neutralizes heparin.

The release of platelet factor 4 during the thrombotic process could possibly play a role in heparin tolerance. Clot retraction results from the contraction of platelet pseudopodia attached to fibrin strands due to the action of actomyosin, which is a contractile protein previously known as thrombosthenin.

Therefore, as a result of adhesion, aggregation and release, a platelt plug forms the initial barrier to prevent haemorrhage, promote vasoconstriction and set the stage to catalyse the coagulation pathways.

The Blood-Clotting Mechanism

Human blood coagulation involves a change from a hydrosol to a hydrogel. During this process thrombin is generated by two pathways, which in turn transform fibrinogen into fibrin threads. forming a mesh for entrapment of various cellular and noncellular components of circulating blood. This process is triggered by blood-vessel injury when normally hidden components of vascular endothelium come into contact with circulating blood.

Blood coagulation is currently considered to represent a cascade phenomenon whereby

initial activation of a plasma protein is followed by a series of autocatalytic proteolytic reactions. Three phases are recognized: the intrinsic, extrinsic and common pathways.

The Intrinsic Pathway

This system may be triggered by the contact activation of factor XII by an altered vascular surface (i.e., subendothelial collagen or a negatively charged surface, such as glass. Promoters of factor XII activation, include prekalikrein (Fletcher factor) high molecular weight kininogen (Fitxgerald factor and factor XI). Serial activation of the intrinsic pathway (XII, XI, IX, VII) culminates in the activation of factor X, the initial step in the common pathway.

The Extrinsic Pathway

In this pathway, the release of tissue factor from injured tissues directly activates factor VII which then activates factor Xa in the presence of calcium. The Ca^{++} complex tissue factor - factor VIII - can activate factor XI.

The Common Pathway

The intrinsic and extrinsic pathways converge on the common pathway to generate activated factor X (Xa). Factor Xa cleaves prothrombin into thrombin. This reaction is catalysed by factor Va (released by activated platelets), by phospholipid (platelet factor 3) and calcium. Once generated, thrombin acts on fibrinogen to release fibrinopeptide A and B (FPA and FPB) and to expose specific sites necessary for fibrin polymerization. Thrombin also activates factor XIII which is able to form cross-linkages between the alpha and gamma chains of the fibrin monomers to form a mechanically stable insoluble fibrin clot.

Fibrinolysis and Thrombin

Fibrinolysis

Once fibrin polymer has been formed and cross linked, it is not easily disrupted. Recanalization and repair of damaged endothelium or the dissolution of fibrin is brought about by the *serine protease plasmin.* This proteolytic enzyme is derived from a circulating inactive precursor plasminogen which is normally converted to active plasmin by two known physiological plasminogen activators, i.e., a plasma plasminogen activator which is activated by factor XIIa, and a vascular (tissue) plasminogen activator (tPA) which appears to be released by venous and capillary endothelium by several stimuli including severe exercise, various states of shock, a number of pharmacological agents (ethylestrenol, stanozolol, adrenaline, vasopressin), venous occlusion and protein C.

Protein C is a vitamin K dependent coagulation inhibitor which enhances endogenous fibrinolysis by the release of tPA. Thrombin is a potent activator of protein C, which therefore initiates coagulation, anticoagulation as well as fibrinolysis.

In the past the most commonly used agents for thrombolytic therapy were the plasminogen activators, streptokinase and urokinase. tPA is now rapidly gaining ground in this

interesting field.

Plasminogen has a marked affinity for fibrin. Activation of plasminogen in the fibrin mesh is a normal physiological clearing mechanism. However, pathological fibrinolysis may occur when there is an excess of circulating plasmin. In this case the plasmin will cause lysis of other proteins such as fibrinogen, prothrombin, vactors V and VIII, ACTH as well as complement. This has considerable significance in the diagnosis and the treatment of secondary fibrinolysis which is commonly associated with DIC.

During fibrinolysis (the sequential proteolysis of fibrin by plasmin) several breakdown products are formed. These are small fibrinopeptides and four large peptides known as X, Y, D and E which are formed in this specific sequence. These fragments have significant anticoagulant properties by virtue of their antithrombin activity, the inhibition of fibrin polymerization and the retardation of the coagulation process.

Fibrin monomer, which is formed as a result of the action of thrombin on fibrinogen, refers to the fibrinogen molecule minus fibrinopeptides A and B. The X and Y breakdown products of fibrin form soluble complexes with fibrin monomer which constitutes the basis for the ethanol gelation, protamin sulphate paracoagulation and ristocetin tests. The ristocetin test becomes positive when there is lysis of intravascular fibrin.

It should be stressed that the byproducts of intravascular coagulation (which are formed as a result of the action of thrombin on fibrinogen as well as the action of plasmin on fibrin) not only provide important diagnostic tools but also contribute markedly to the haemostatic breakdown which is already compromised by the consumption as well as the fibrinolytic breakdown of various coagulation factors. Furthermore these paracoagulable monomer complexes appear to block the microcirculation - a significant cause of organ failure in cases of advanced DIC.

The Clinical and Laboratory Assessment of Haemostatic Function

A bleeding tendency may be congenital or acquired. The evaluation requires exclusion of vascular disorders, platelet abnormalities, factor deficiencies or multiple defects.

Clinical Evaluation

The most important features in the evaluation of the surgical patient as a haemostatic risk are a careful history and a thorough physical examination. A personal, family and drug history may give an indication of the nature of the defect. Whereas a vascular or platelet abnormality usually presents with purpura or mucosal bleeding, patients with a factor deficiency usually have a history of prolonged bleeding after injury, tooth extraction, confinement or an operation. Bleeding into joints and soft tissues rather than mucosal bleeding is the rule. Excessive menstrual flow rather than intermenstrual bleeding may be a feature of haemostatic incompetence - usually a platelet disorder.

It is rare for a bleeder to present with isolated gastrointestinal bleeding without other evidence of bleeding. A detailed drug history is essential. Aspirin has a profound effect on platelet function: intraoperative haemostatic failure in a heparinized patient may be the first

indication of an aspirin-induced quantitative platelet defect.

Special care should be taken with a family history. Such information may be invaluable in detecting a mild factor VIII deficiency, where inadequate preoperative preparation may have disastrous consequences.

During examination of the patient a special search should be made for petechiae, ecchymoses, and telangiectasia. Areas such as the throat, oral cavity, limbs and breasts should be carefully scrutinized. Persistent oozing or ecchymoses at venepuncture sites, enlarged lymph nodes, hepato-splenomegaly and jaundice should be recorded. A haemorrhagic tendency may be the presenting symptom of a serious underlying disease (i.e. disseminated cancer, liver failure or end-stage renal disease). It is therefore of cardinal importance to interpret the various screening tests for haemostatic competence in conjunction with a careful medical history, a thorough clinical examination and a full blood count.

Laboratory Investigations

Bleeding Time

The bleeding time is a measure of the integrity of the vascular and platelet components of haemostasis. A prolonged bleeding time is found with quantitative and qualitative platelet disorders or a microvascular structural defect. Bleeding time is the time required for bleeding to stop after a standardized superficial incision is made in the forearm. The template modification of the Ivy method is preferred in most laboratories. The Mielke apparatus ensures a reproducible wound in the forearm 5 mm long and 1 mm deep.

It is essential that the time between inflation of the upper arm sphygmomanometer cuff to 40 mm Hg and the incision should not exceed 60 seconds. Oozing blood is gently absorbed onto filter paper at 30 seconds intervals until the bleeding stops. A normal bleeding time using the template method is less than 9 minutes.

The patient should be carefully questioned about the use of aspirin or other antiplatelet agents.

Prolonged bleeding times are generally related to quantitative or qualitative platelet defects. As a rule the bleeding time will not be prolonged until the platelet count drops below 100000 per cubic millimetre unless there is a disorder of platelet function.

Abnormal platelet function may be associated with renal failure, dysproteinaemic states, liver cirrhosis, leukaemia and rarely in a congenital disorder called thrombasthenia, platelet release abnormality or storage pool defect. Functional platelet disorders may be caused by inadequate platelet aggregation or a defective release of essential factors to the haemostatic profile.

Aspirin will prolong the bleeding time for the lifespan of the platelets which is about one week.

Other tests of platelet function include the tourniquet test, platelet evaluation on a

blood smear, platelet aggregation studies, the release of platelet factors and betathromboglobulin in response to stimulation with epinephrine, collagen and arachidonic acid. Thromboelastography also provides a reliable assessment of platelet function.

Coagulation Studies

The whole-blood clotting time is an insensitive test and should not be used as a screening test to detect a bleeding tendency.

The Activated Partial Thromboplastin Time (APTT)

The APTT is a screening test for the intrinsic and common coagulation pathways. Therefore only factors VII and XIII are not tested.

The APTT test is performed by mixing platelet-poor plasma with a phospholipid emulsion which serves as a platelet substitute. The platelet substitute serves as a "partial" thromboplastin which activates only the intrinsic pathway.

The APTT is sensitive in detecting abnormalities of the intrinsic pathway, especially haemophilia A and B (factors VIII and IX deficiencies) and is at present the most widely used test as a monitor of heparin therapy.

Prothrombin Time (PT)

The PT measures the extrinsic and common pathways. Thromboplastin is added to platelet-poor plasma and the coagulation time is recorded. At present concerted efforts are being made to standardize the thromboplastin used in this test. The results are expressed as the prothrombin ratio which is derived from the PT of the patient divided by the PT of pooled plasma from normal controls. The normal value would therefore be 1. The generally accepted therapeutic range for oral anticoagulant therapy lies between 2 and 4. A prolonged PT is usually drug-induced or associated with liver disease.

Thrombin Time (TT)

The TT is determined by adding thrombin to plasma. Coagulation usually occurs within 15 seconds. The test is influenced by the structure and concentration of fibrinogen and by the presence of coagulation inhibitors (heparin, FDP, lupus anticoagulant) and represents the penultimate step in the common pathway.

The thrombin clot lysis time is a useful byproduct of the thrombin time, and is used as a rapid screening test to exclude hyperfibrinolysis. The clot derived from the test for estimating the thrombin time is placed in a water bath at 37 $ÄC. Clot lysis within 5 minutes signifies a hyperfibrinolytic state. Definitive tests for plasma fibrinolytic activity include euglobulin lysis time (ELT), lytic zones on fibrin plates, and plasminogen, plasmin and activator assays. However, although these tests are useful in a preoperative work-up, they are of limited value in an emergency.

Thromboelastography

The thromboelastogram is a mechanically operated optical system which provides a continuous visual observation of all the phases of coagulation. The resulting recording, which is termed a thromboelastogram (TEG), represents a graphic resumé of coagulation and fibrinolysis or the time and degree of the interaction between the activators and inhibitors of both systems. The TEG offers a simple, reliable method of defining the key areas of haemostatic incompetence or for assessing the efficacy of a therapeutic programme. Thromboelastographic hypercoagulability, which has deservedly been given prominence in the recent literature, adds an interesting dimension to the diagnostic spectrum of an instrument which, after an initial capital outlay, runs at exceptionally low cost.

The TEG consists of two or three cylindrical cuvettes of chrome-nickel steel which are thermostatically controlled at 37 °C. Each cuvette containing the blood sample is rotated to and fro around a vertical axis over an angle of one-twelfth radian. A piston of the same material is lowered by means of a torsion wire into the cuvette, leaving a one millimetre space which contains the blood or plasma sample. The oscillations of the torsion wire are represented as a direct visual readout on a strip of recording paper.

As long as the blood sample remains fluid, the piston will remain motionless. As soon as fibrin strands are formed in the specimen, the oscillations will be transferred to the piston and hence to the torsion wire and the recording device.

The tracing has three basic components: the r-time which represents the clotting time, the k-time which corresponds to the rate of fibrin build-up and the ma which expresses the maximal elasticity of the coagulum (fig. 3.10.3) (normal TEG).

Although the TEG is not capable of identifying a vascular defect, it has been shown to be a most reliable screening procedure for identifying the unsuspected bleeder or defining the key area of defective haemostasis which may then be explored in more detail. The instrument can be transferred to the critical care unit or operating room where the efficacy of component therapy or pharmacological manipulation can be assessed in a matter of minutes. Various thromboelastographic patterns are shown in figure 3.10.3.

Screening for Disorders of Blood Coagulation

A prolonged template bleeding time (TBT) suggests a vascular or platelet defect. In marginal vascular or platelet defects, the aspirin tolerance test (ATT) may be conclusive.

Quick demonstrates that whereas normal subjects showed only a marginal increase in the bleeding time two hours after taking two aspirin tablets (650 mg), patients with minor von Willebrand syndrome showed a significantly prolonged bleeding time after aspirin, signifying an abnormal ATT. An abnormal TBT and ATT with a normal platelet count suggests a vascular or qualitative platelet defect. If the platelet function studies are normal, the bleeding disorder is probably related to vascular dysfunction. A prolonged PTT and PT is usually associated with liver disease or drug administration. An abnormal PTT and normal PT in a patient with a family history who is not receiving any medicament suggests one of the haemophilioid syndromes (classical haemophilia VIII, Christmas disease (IX) and Rosenthal syndrome (XI)). Von Willebrand's disease, one of the common inherited bleeding disorders affecting both sexes, presents as a double defect, i.e. abnormal platelet adhesion (prolonged

TBT) in combination with a low factor VIII procoagulant activity (prolonged APTT).

Fortunately, the other inherited bleeding disorders are extremely rare (I, II, V, VII and X). Furthermore, bleeding owing to these defects is usually so severe that the diagnosis is usually made at an early age. Factor XIII deficiency which may present with prolonged bleeding or poor wound healing after operation is characterized by a spindle-shaped TEG similar to those found in fibrinolytic states.

The TEG tracings associated with a circulating anticoagulant, a platelet defect, abnormal lysis or hypercoagulability are quite distinctive. Conversely, abnormal bleeding associated with a normal TEG points to a vascular abnormality.

Multiple coagulation defects are often drug-induced or are found after trauma, in major surgery in cases of advanced malignancy, and in liver disease. In cases of liver disease there is a decline in factors I, II, V, VII, IX and X as well as antithrombin III. Cirrhosis of the liver is often associated with hyperfibrinolysis. Hypersplenism may give rise to thrombocytopenia. In cases of obstructive jaundice, the factor V levels are usually normal and the haemostatic defect is correlated after the administration of vitamin K.

Prospective Haemostatic Evaluation

Often intra- or postoperative haemostatic breakdown could have been **prevented** had the defect been identified before the operation. Surgical trauma combined with blood transfusion and the administration of various pharmacological agents may transform a minor defect into overt haemostatic failure.

The patient should be carefully questioned about the family history and the ingestion of medicaments, especially those containing aspirin. The legislation of prothrombin-depressing agents taken with aspirin, other antiplatelet drugs, antihistaminics and non-steroidal anti-inflammatory agents may result in sudden, serious, unexpected and uncontrollable intraoperative haemorrhage. In cases where an emergency operation has to be performed in the face of a qualitative platelet defect, at least 8 units of platelet concentrate should be administered immediately prior to operation, again in the recovery room and daily thereafter for two days.

As a general rule, patients on well-controlled prothrombin depressing agents are usually haemostatically competent and, if they have not been taking antiplatelet agents, can safely undergo an abdominal operation provided that the preoperative TEG shows haemostatic competence, careful attention is given to technical detail and fresh frozen plasma is available immediately on demand.

Furthermore, those cases with mechanical heart valves should not be subjected to vitamin K1 reversal before the emergency, in view of the real danger of intracardiac thrombosis.

Intra-Operative Haemostatic Failure

When unexpected bleeding occurs during an operative procedure it is essential to

determine whether this is related to a nonmechanical cause. Bleeding from multiple sites or a generalized ooze from the operative field is suggestive of a haemostatic defect.

A laboratory screen should include a TEG, platelet count, PTT, PT, TT and thrombin clot lysis time (TCLT): a TCLT of less than 5 minutes denotes hyperfibrinolysis.

Since a platelet defect is the most common cause of haemostatic breakdown in the surgical patient, severe intra-operative bleeding should be treated empirically with platelet concentrates. If bleeding is severe, a minimum of 8 units (1 unit = 30 mL) should be infused as rapidly as possible. This represents the platelet equivalent of 8 units of whole blood.

Further management will depend on the results of the screening profile. Useful therapeutic protocol is summarized in table 3.10.1.

Regular TEG determinations are done to assess the efficacy of the therapeutic programme.

Table 3.10.1. Therapeutic options

Platelet defect	Platelet concentrate (administer platelets prophylactically after 10 units of banked blood)
Factor deficiency	Fresh frozen plasma Cryoprecipitate Specific factor concentrates
Coumarin or Warfarin excess	Fresh frozen plasma Cryoprecipitate Vitamin KI (to be avoided in cases of heart-valve replacement)
Heparin excess	Protamine reversal (Protamine may act as an anticoagulant)
DIC	Treat cause Minidose heparin Component therapy
Hyperfibrinolysis	Exclude DIC Antifibrinolytics rarely indicated
Haemolytic reaction (incompatible blood transfusion)	Important cause of unexplained bleeding Standard measures Treat DIC

Disseminated Intravascular Coagulation (DIC)

DIC or defibrination is defined as a clinical pathological syndrome of variable expression in which the formation of fibrin thrombi, the consumption of specific plasma proteins, the loss of platelets and the activation of the fibrinolytic system suggest the presence of thrombin in the systemic circulation. However, according to more recent conceptions DIC is better defined as a syndrome resulting from the uncontrolled simultaneous activation of the coagulation and fibrinolytic systems with the formulation of soluble monomer complexes.

Pathogenesis

Activation of the coagulation pathways may occur in several ways. Thromboplastin or procoagulant material from traumatized, infarcted or malignant tissue, amniotic fluid or the placentalsite may trigger the coagulation sequence. Defibrination may be associated with viraemia, rickettsial infections, snakebite and gram-positive and endotoxic shock. Septicaemia probably induces coagulation by exposed subendothelial collagen as well as by initiating platelet release. The final common pathway relates to thrombin which not only transforms fibrinogen to fibrin but triggers the fibrinolytic pathway by activating plasminogen or profibrinolysin.

The Clinical Diagnosis of DIC

DIC should be suspected when a bleeding tendency follows on extensive trauma, shock, sepsis, intravascular haemolysis, obstetrical accidents or cancer. It is essential to maintain a high index of suspicion when bleeding from several sites, thrombosis, acrocyanosis, shock, hypoxia and multiple organ failure occur in the appropriate clinical setting.

Laboratory Diagnosis

In essence the laboratory diagnosis of DIC is related to the activation of the clotting mechanism, the consumption of platelets and various clotting factors (notably I, II, V, VIII, XIII and antithrombin III), an activated plasmin system, the production of the proteolytic cleavage products of fibrinogen and fibrin, abnormal blood-cell morphology, the histological evidence of fibrin thrombi and skin necrosis.

The TEG Transfer Test

Complementary to the thromboelastographic picture of recalcified citrated whole blood, the thromboelastographic transfer test, which is carried out on citrated platelet-rich plasma, is used to identify procoagulant activity (fig. 3.10.3). The r-value of a control iso-group plasma is compared with the r-value of a mixture of equal parts of the control plasma and the patient's plasma. The result is given by the ratio

r-mixture / r-control.

Normal values are between 1 and 1.5. Low values indicate procoagulant activity in the patient's blood. A value above 1.5 indicates heparin excess.

The thromboelastographic transfer test provides a rapid method for the control of therapy in cases of DIC, where the heparin requirements may be accurately determined by titration within a matter of minutes. By combining the whole-blood thromboelastograph with the transfer test, it is therefore possible to identify procoagulant activity in a blood sample which may be paradoxically hypocoagulable as a result of the consumption of coagulation factors or the presence of breakdown products which have anticoagulant properties in their own right.

Careful monitoring of heparin therapy is mandatory in these cases. By potentiating the natural inhibitor of factor X, small doses of heparin neutralize activated factor X, thereby preventing further consumption. By the transfer test, the heparin dosage may be titrated to the nearest 50 units per hour. This additional diagnostic parameter provides a simple and practical method of prescribing a potentially lethal agent with reasonable confidence in a highly complex situation where several diagnostic and therapeutic variables are involved. The laboratory diagnosis of DIC is summarized in table 3.10.2.

Primary fibrinolysis is less common than DIC and is seen only in certain tumours such as carcinoma of the lung and prostate, electric shock and in chronic liver cirrhosis. Although DIC may develop in liver cirrhosis it is usually limited to those patients in whom there is shock or sepsis. Thrombocytopenia is unusual in primary fibrinolysis, and the pera-coagulation and restocetin tests are usually normal. However, differentiation may be difficult.

Table 3.10.2. The laboratory diagnosis of DIC

Coagulation defect	*Test*
Activation of the clotting mechanism (intravascular conversion of fibrinogen by thrombin)	+Soluble monomer complexes (protamin sulphate ethanol gelation and ristocetin tests)
	Hypercoagulable TEG
	TEG transfer test
Consumption of platelets (thrombocytopenia)	Platelet count
	TEG
Consumption of coagulation factors	Prolonged PT
	Prolonged APTT
	Prolonged TT
	Low fibrinogen
	Depressed factors V, VIII, AT III
	TEG
Activated plasmin system	Shortened TCLT (less than 5 min)
	Shortened ELT
	Shortened whole-blood clot lysis time (WBCLT)
	Presence of fibrin degradation products (FDP)

Abnormal blood morphology	Red-cell fragmentation (schistocytosis)
Skin histology	Fibrin thrombi and skin necrosis

Management of DIC

The first echelon of therapy is directed at removing the precipitating cause which is responsible for the release of procoagulant activity into the circulation, i.e. removal of necrotic or malignant material, the evacuation of a dead foetus, the drainage of an abscess or aggressive treatment of gram-negative shock. Additional supportive measures include fluid and electrolyte replacement, correction of acid-base disturbances, antishock measures and antimicrobial therapy.

If bleeding continues and the laboratory screen supports the diagnosis of thrombin release with intravascular coagulation and the consumption of clotting factors, several leaders in the field hold the view that it is advisable to stop further consumption by instituting heparin therapy. Although world opinions appears to be divided, experience has shown that provided that minidose heparin therapy is instituted before irreversible consumption occurs, continuous heparin infusion given in an accurate dosage under strict control (TEG transfer test) will inhibit the thromboplastic assault and curtail the consumption. The average mini-heparin dosage required is approximately 300-500 units per hour. The continuous heparin infusion method lends itself to a therapeutic programme whereby titrations are carried out at hourly intervals if necessary depending on the urgency of the situation and the degree of coagulability.

Depleted clotting factors may be replaced by using fresh frozen plasma, cryoprecipitate and platelet concentrates. The administration of platelet concentrates is especially indicated in those cases where the thrombocytopenia is complicated by a qualitative platelet defect. Replacement of antithrombin III may also be required.

Fibrinolytic inhibitors such as cyclocapron are not without danger and are almost never indicated. In view of the possibility of massive thrombosis as a result of inhibition of the fibrinolytic defence mechanism, fibrinolytic inhibitors should be used only under adequate anticoagulant cover, i.e. heparin. Oral anticoagulants cannot be substituted for heparin in the treatment of DIC.

Factor VIII Deficiency

Classical Haemophilia (Haemophilia A)

Haemophilia A, the most common severe inherited coagulation disorder, is transmitted as a sex-linked recessive trait. In 70% of cases there is a positive family history of affected males. A high mutation rate explains the remaining 30%.

Although severe haemophiliacs may bleed shortly after birth, the malady usually presents during childhood with haemarthrosis, muscular, sublingual or submucous haematomas, epistaxis or protracted bleeding after trivial injuries. Bleeding in the vicinity of vital structures may be life threatening.

The laboratory screen shows an abnormal PTT, normal PT and normal template bleeding time. The abnormal PTT may be corrected by the addition of normal plasma.

Replacement therapy to raise the factor VIII levels to haemostatic levels form the basis of treatment. One millilitre of normal plasma contains 1 unit of factor VIII. The level in fresh frozen plasma drops to 0.60 units. Cryoprecipitate contains about 10 units of factor VIII activity per millilitre. Antihaemophilic factor AHF provides factor VIII in concentrated form (expressed in units).

Factor VIII, being a liable factor, has a half-life of 8-12 hours. Therefore replacement therapy should be given 12-hourly and maintained for at least 10 days or up to four weeks when wound healing is complete and all signs of haemorrhage have ceased. Treatment schedules are calculated according to the patient's body mass, the severity of the bleeding and the desired factor VIII level to control each type of haemorrhage.

The daily dose of factor VIII (units per kilogram) to raise the plasma factor VIII to haemostatic levels will be approximately 10-20 for a minor haemorrhage, 20-30 for a severe haemorrhage and 30-40 for major surgery. This regimen will raise the plasma factor VIII levels to 10-20%, 30-50% and 50-70% respectively. Interested readers will find the detailed directives by Cronberg on the management of haemophilia most erudite and instructive.

It is of fundamental importance to raise the plasma factor level before embarking on any invasive procedure. Even the removal of sutures or dental work in close proximity to the alveolus is not without risk. Attempted correction after the onset of haemostatic breakdown may lead to disaster.

For milder haemophiliacs or during episodes of less severe haemorrhage, cryoprecipitate may suffice. Cryoprecipitate has a decreased risk of hepatitis. Cyclocapron may diminish bleeding after dental procedures. **It is imperative to warn the patient against the use of all medicaments containing aspirin or non-steroidal anti-inflammatory agents. Defective platelet function may precipitate a major bleeding episode.** The presence of factor VIII antibodies is of serious importance and requires highly specialized treatment (plasmapheresis, etc).

Local treatment should be limited to ice packs and immobilization. Aspiration of joints and the evacuation of haematomas are considered to be major surgical procedures requiring full replacement therapy for at least 10 days. These **invasive measures** are preferably avoided.

Complications include AIDS, haemorrhage, hepatitis, development of deformities and hypertension. Fatal haemorrhage is still considered to be the major cause of death.

Comment

Haemostasis

A. du P. Heyns

Although a platelet plug is sufficient to arrest bleeding in capillaries and small venules, it has to be rapidly reinforced with fibrin to effectively arrest blood loss from larger vascular lesions. The interaction of platelets with coagulation factors is central to the understanding of this process. The end point of a chain, or cascade, of enzymatic reactions, in which a proenzyme is activated to an enzyme which in turn activates another pro-enzyme, culminates in the formulation of a platelet plug.

These clotting factors (pro-enzymes) are present in the fluid phase of blood. However, the concentration of clotting factors is markedly accelerated by their being absorbed and concentrated onto surfaces. It is important to consider coagulation as a series of surface-catalysed events. The blood platelets are the major supply of such surfaces for coagulation reactions. The activated platelet provides a phospholipid surface on its membrane; this is ideal for the activation of factor VII and factor X in the presence of membrane-bound activated factor V. The view that phospholipid is released by the platelet (platelet factor III) is therefore not tenable from a conceptual point of view. The process should rather be considered as an alteration of the platelet membrane which occurs after activation of the platelet. Thrombin, generated by the coagulation cascade, exposes phosphatidylserine on the platelet membrane. This "flip-flop" reorientation of membrane phospholipids permits factor IXa to be brought into correct spatial alignment with factor X. Factor X can then be activated in the presence of activated factor VIII.

The common pathway of the extrinsic and intrinsic coagulation systems begins with factor Xa. The catalysing property of factor Xa is dramatically enhanced in the presence of factor V and phospholipid. Factor V is bound firmly to the phospholipids of the platelet membrane and serves as a co-factor for the rapid conversion of prothrombin to thrombin.

A tissue lipoprotein is involved in the activation of the extrinsic coagulation pathway. This complex is known as tissue thromboplastin. When the tissue factor comes into contact with blood, the factor X in the plasma, in the presence of calcium ions and with the help of the gamma-carboxyglutamic acid, readily fixes to the phospholipid component of the tissue factor. Factor VII rapidly activates the factor X molecule bound on the phospholipid complex.

Substances which control the concentration of activated coagulation factors are important in controlling the extent of thrombosis. The principle physiological function of fibrin is to plug lesions through which blood is seeping. As soon as this is achieved, a mechanism must be triggered to prevent the uncontrolled formation of excess fibrin. Since blood coagulation reactions take place on negatively charged surfaces, mainly on platelets, fibrin formation tends to be localized to the site of vessel injury. Blood flow will tend to wash away the unbound coagulation factors and the resultant haemodilution will limit the formation of fibrin to the site of injury. Several plasma proteins, which inhibit various stages of the coagulation sequence, also play a supportive role. The most important of these substances is antithrombin III, which neutralizes antithrombin and other serine proteases such as factors Xa,

IXa, XIa, XIIIa and kallikrein.

Protein C provides further defence against uncontrolled fibrin formation. It is a pro-enzyme whose synthesis is dependent on vitamin K. It is activated by thrombin into a serine protease which can inactivate factors Va and VIIIa and inhibit the binding of factor Xa to platelets. The action of protein C is facilitated by another vitamin K dependent protein, protein S.

Other less important inhibitors of blood coagulation are alpha-II macroglobulin, CI-inhibitor, and alpha-I antitrypsin. Although deficiencies of antithrombin III, protein C and protein S predispose to thrombosis, the other inhibitors are of limited clinical importance.

A logical approach to the preoperative evaluation of haemostasis has been proposed by Rapaport. Although the thromboelastograph has proved to be a useful diagnostic tool in the hands of a few experts, it has not found general approval with haematologists. The clinician will therefore have to depend on the other, more readily available, laboratory tests used for the evaluation of platelet function, the intrinsic and extrinsic coagulation mechanisms and the fibrinolytic system.

- The screening questionnaire should initially focus on the family history; the duration and pattern of bleeding after tooth extraction or operations; presence of other diseases; concomitant medication; and the necessities of transfusion therapy to control haemorrhage.

- If the screening history is negative and minor surgery is contemplated, no laboratory tests are required.

- If the screening history is negative and major surgery is envisaged, a partial thromboplastin time (PTT), prothrombin time (PT) and platelet count are recommended.

A screening history suggestive of a haemostatic defect requires evaluation of the adequacy of the formation of a platelet plug (bleeding time); adequacy of blood coagulation (PTT and PT); and evaluation of the stability of the fibrin clot (clot lysis time: factor VIII). If these test results are negative and the history is very suggestive of a haemostatic defect, the bleeding time after 600 mg aspirin; assay of factors VIII, IX and von Willebrand factor; and a thrombin time are indicated.

The further investigation of patients with positive screening laboratory tests will usually elucidate the prime defect. It should be noted that reduced levels of a contact activation factor is the most common cause of a prolonged PTT. Factor XII, prekallikrein or high molecular weight kininogen deficiency is of no clinical importance. However, factor XI deficiency requires replacement therapy if extensive surgery or a severe haemostatic challenge (i.e. prostatectomy) is contemplated.

Comment

Haemostasis

E. J. Immelman

This chapter and overview of haemostasis in the surgical patient leaves little unsaid. However, three areas deserve comment.

Use of Thrombo-Elastography

This apparatus has been decried by some traditional haematologists as being imprecise. However, an increasing number of intensive care units and operating theatre suites find it a rapid and useful test for the initial screening of a haemostatic problem, for the control and reversal of heparin therapy, for the diagnosis and treatment of DIC and for the management of certain snake bites. Many teaching hospitals in South Africa do not have access to thrombo-elastography. It deserves wider application.

Aspirin and The Surgical Patient

Aspirin produces a powerful inhibitory effect for the entire lifespan of circulating platelets exposed to the agent. For most categories ofsurgery aspirin does not require to be stopped preoperatively. However, patients taking aspirin should stop 14 days preoperatively if undergoing a neurosurgical procedure, major liver surgery or aortic surgery in which a knitted dacron graft is to be employed. In this latter situation bleeding through the graft may be of sufficient magnitude to require platelet transfusion.

Balanced against the risk of increased bleeding in patients on aspirin is recent evidence to suggest that pretreating patients who are about to undergo coronary artery bypass grafting or femoro-popliteal bypass with aspirin and dipyridamole will reduce the risk of early graft thrombosis.

The "Hypercoagulable" State

There are now a number of well-established clinical conditions which are associated with an increased tendency to either arterial or venous thrombosis. Surgeons require to be aware of these conditions as surgery on such patients may be associated with an unacceptable incidence of venous thrombo-embolism.

These include:

- congenital thrombophilia

- congenital dysfibrinogenaemia

- congenital anti-thrombin III deficiency

- congenital protein C or S deficiency

- homocysteinuria

- sickle-cell disease

- acquired thrombocytosis (i.e. after splenectomy)

- lupus anticoagulant

- paroxysmal nocturnal haemoglobinuria

- malignant disease

- oestrogens and oral contraceptives

- heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia, previously thought to be rare, is now known to occur in 0.6-10% of patients exposed to heparin. It is more likely to occur with therapeutic heparin but it has been described after exposure to low doses of heparin. The syndrome is caused by a complex of IgG and heparin which causes intravascular platelet aggregation. The syndrome is characterized by marked thrombocytopenia, haemorrhage and paradoxical arterial and/or venous thrombosis. These life- or limb-threatening complications have resulted in quited major morbidity of 22-61% and a mortality of 12-23%.

Platelet counts should be obtained daily in all patients who have received or are receiving heparin. If the platelet count falls below 100000/mm^3 all heparin is discontinued and the serum tested for the presence of heparin-dependent anti-platelet antibodies. If the test is positive all heparin must be discontinued and the patient placed on aspirin and dypyridamole. If continued anticoagulation is required, warfaring should be used.

Chapter 3.11: Venous Thrombosis and Pulmonary Embolism

R. C. Franz

Although pulmonary embolism is the third most frequent cause of death in the USA, the diagnosis is missed in over 70% of cases. Yet in a recent survey involving 752 orthopaedic and 663 general surgeons with a response rate of over 70%, it transpired that routine prophylaxis was offered in only 28% of hip fractures, 48% of hip replacement and 62% of general surgical cases. These findings suggest that available figures remain unconvincing to practising in the UK. However, at a recent National Institute of Health consensus development conference, the majority opined that several methods of prophylaxis can reduce the risk of venous thrombosis and evidence that such therapy can prevent pulmonary embolism has been characterized as "compelling".

Pathogenesis

Since 1854 when Virchow propagated his famous thrombogenic triad, it has been widely assumed that stasis or retarded blood flow, intimal damage and hypercoagulability are causally related, individually or in combination, to venous thrombosis.

Stasis

Stasis, which appears to be a facilitating rather than an initiating factor, predisposes to venous thrombosis in several ways. It facilitates the interaction of blood elements with the vessel wall, and prevents the clearance of activated factors by the liver and the mixing of activated factors with the inhibitors. Although experimental venous thrombosis can readily be evoked by a combination of stasis and endothelial damage or hypercoagulability, this is not the case with experimental stasis alone.

Intimal Damage

When Virchow propagated his famous triad, the main function of venous endothelium was thought to be that of a flow surface. However, several important antithrombogenic functions attributed to venous endothelium have since been documented, viz. electrostatic repulsion by a negatively charged surface, a cover for subendothelial connective tissue components which are highly thrombogenic (collagen, elastin, glycosaminoglycans) and the synthesis of prostacyclin (PGI2), a potent platelet antiaggregating agent and a potent source of plasminogen activator. Furthermore, the lumenal surface of the endothelium is lined by an endocapillary layer, the glycocalyx, which is composed of polysaccharides and heparan sulphate. Heparan sulphate is structurally similar to heparin and probably inhibits blood clotting.

Normal intact endothelium is non-thrombogenic but when the intima is damaged by chemical or mechanical trauma, immune complexes, endotoxin, viruses or bacteria, a breach in the endothelial lining exposes subendothelial collagen. Collagen which activates factor XII is also a potent platelet-aggregating agent. An intimal defect with stripping of endothelial cells, disruption of the basement membrane, exposure of subendothelial collagen fibres and the formation of a primary platelet thrombus and secondary fibrin, can readily be demonstrated by scanning electron microscopy of the venous lumenal surface. Similarly, following both physiological and pharmacological stimuli, leukotriene B4 (LTB4), which is the most potent chemotactic factor derived from the metabolism of cell membrane phospholipids via an intracellular pool of arachidonic acid, can act in concert with other chemotactic factors to enhance migration of granulocytes into extravascular sites both directly and via its ability to increase vascular permeability. Leucocytes therefore rapidly accumulate in the subendothelium leading to further damage, and the release of thromboplastin and various proteases.

Hypercoagulability

The hypercoagulable states has been defined as any laboratory or clinical abnormality that is pathogenetically associated with an increased tendency to thrombosis.

Several factors have been implicated in the hypercoagulable state. The most important are changes in platelet adhesiveness, increased content of one or more coagulation factors, decreased content of inhibitors in the coagulation system, decreased fibrinolytic activity and increased content of inhibitors of fibrinolysis and increased content of serum lipids. Primary hypercoagulable states include antithrombin III and protein C deficiency, defective fibrinolysis and homocystinuria. Secondary hypercoagulability is associated with malignancy, the postoperative period, immobilization, obesity, hormonal contraception, pregnancy and the puerperium, the nephrotic syndrome, diabetes mellitus and rare haematological disorders such as myeloproliferative disorders, polycythaemia and Waldenström's macroglobulinaemia.

The Diagnosis and Treatment of Venous Thromboembolism

Superficial thrombophlebitis usually presents with the symptoms and signs of inflammation over the course of a superficial vein. It is often associated with varicose veins. Unexplained repeated attacks of thrombophlebitis, especially in young patients, should raise the suspicion of a hypercoagulable state.

Superficial thrombophlebitis should be differentiated from lymphangitis, cellulitis, haematoma, bruising, ruptured plantaris tendon, or erythema nodosum. The condition may accompany deep vein thrombosis.

Treatment is usually nonoperative with elevation, hot compresses and aspirin, or walking with an elastic support. Anticoagulants are not required as pulmonary embolism is extremely rare. However, propagation from the saphenous into the femoral vein has been reported. This complication may be prevented by proximal ligation of the saphenous vein.

In recalcitrant or recurrent cases a more aggressive approach is required. Excision is curative.

Deep Venous Thrombosis

The clinical diagnosis of deep-vein thrombosis is notoriously unreliable. The pattern of venous thromboembolism in a surgical ward shows that approximately 33% of patients have a positive 125I fibrinogen test in the calf. Of these only one-third (or 10% of all surgical patients) will develop clinical symptoms or signs of embolism, but 0.2% will succumb to a fatal event. After hip surgery this figure may be 10 to 20 times higher. Conversely, it has also been shown by venography that half of the patients with clinically suspected thrombosis have normal veins.

In an excellent study supported by univariate and multivariate analysis Nicolaides *et al* compiled a list of maximal likelihood estimates the usual clinical symptoms and signs.

Of the symptoms and signs studied, leg swelling, proximal extension of symptoms and

signs, deep induration in the calf muscles, oedema distal to the knee, positive Homan's sign, thigh tenderness and oedema were associated with a high incidence of deep-vein thrombosis. However, none of these signs are diagnostic because they can be simulated by several other conditions such as other causes of oedema, cellulitis, haematoma, exertional rhabdomiolysis or a ruptured Baker's cyst, popliteal aneurysm or calf muscle (i.e. **Musculus plantaris**) lymphatic obstruction, peripheral disease or neurogenic pain. Advanced iliofemoral venous thrombosis presents with a massively swollen cyanosed limb - àphlegmasia caerulea ßÑ which may progress to venous gangrene. Proximal venous thrombosis ßÑ ociated with arterial spasm and a "white" leg or àphlegmasia alba ßÑ Deep venous thrombosis may be completely asymptomatic or present ßÑ al pulmonary embolism.

Special Investigations

Contrast Phlebography

Accurately performed ascending phlebography remains the reference standard of the diagnostic spectrum. The investigation is done by injecting contrast medium into a small vein on the dorsum of the foot. With the patient in a 40 degrees foot down-position, excellent visualization of the deep system can be achieved up to the groin. Venous thrombi are shown as constant sharply demarcated filling defects on different views. However, false positive results may be caused by tensing of muscles, incomplete mixing of dye or underfilling.

Complications are well documented, but fortunately these are rare: pain, swelling, erythema and extravasation of contrast material and very rarely pulmonary embolism. To minimize complications the venous system should be flushed with heparinized saline after completion of the phlebogram.

The fundamental practical issue is whether a venogram should be done in every case of clinically suspected thrombosis. Although several influential authors support this view, others feel that this practice would impose an undue burden on the radiologist. In the patient who is not taking hormonal contraceptives and who has limited calf tenderness only, serial ultrasound and Doppler studies on an outpatient basis will probably suffice. Small single thrombi confined to the calf rapidly undergo lysis if the patient wears well-fitting stockings and remains ambulant.

Impedance Plethysmography

In 1971 Wheeler and Mullick introduced the technique of electrical impedance plethysmography (EIP) for the diagnosis of deep-vein thrombosis. Proximal deep-vein occlusion decreases the lower-limb volume changes which are brought about by intermittent compression by means of a thigh cuff. The volume changes cause alterations in electrical impedance (resistance) which can be accurately quantified on a recorder. This non-invasive method is most suitable for proximal (iliofemoral) occlusive lesions.

Doppler Ultrasound

The frequency of a sound beam emitted by the Doppler ultrasound blood velocity detector is altered by the moving cellular compounds in the bloodstream. Although Doppler studies are as reliable as EIP in the diagnosis of proximal occlusive lesions, the instrument is unreliable in major distal thigh or calf vein thrombosis.

Radionuclide Studies

Isotope pharmaceuticals may be used to demonstrate venous thrombi. Two basic principles are utilized. Certain substances such as fibrinogen, plasmin and plasminogen activators which have an affinity for fibrin are labelled with a radiopharmaceutical which is then incorporated into the thrombus. 125I fibrinogen has been widely used in the detection of postoperative venous thrombi. The isotope is injected pre-operatively and the legs are serially scanned with a portable scintillation counter for "hot spots" which signify the incorporation of the isotope at the site of thrombus formation. The test is unsuitable for the detection of established DVT as counting is usually done 24, 48 and 72 hours after injury. Furthermore the test is positive where fibrin is deposited as part of the inflammatory response to mechanical, thermal, infective or other trauma.

Radionuclides may also be used to demonstrate venous filling defect or impairment of blood flow. The use of 99mTc human serum albumin microspheres is a simple and reliable method for the detection of venous thromboembolic disease. Simultaneous visualization of the peripheral and central venous system is followed by perfusion imaging of the lung fields. Agreement between RNV and contrast venography appears to vary from 76 to 96%.

The Prophylaxis of Postoperative Venous Thromboembolism

Measures Directed Against Hypercoagulability

Low-Dose Heparin (LDH)

Since 1962 when the concept of perioperative LDH was introduced by Sharnoff, the efficacy of LDH as a prophylactic agent against postoperative DVT has been evaluated in several randomized trials. The most comprehensive international multicentre trial to assess the efficacy of LDH against fatal postoperative pulmonary embolism was organized by V. V. Kakkar of King's College Medical School and conducted in 28 centres (2076 controls versus 2045 patients receiving LDH). Patients in the treatment group received 5000 units of calcium heparin in the subcutaneous fat of the anterior abdominal wall two hours preoperatively and every eight hours thereafter for seven days or until the patient became ambulatory. These findings showed that LDH reduces the incidence of postoperative pulmonary embolism significantly, but other influential authors opine that although LDH reduces the incidence of postoperative DVT, there appears to be no change in fatal pulmonary embolism. However, despite this controversy there is reliable evidence that LDH prophylaxis is effective in moderate-risk patients.

In view of the fine studies of Wessler who has shown that small doses of heparin can potentiate the activity of factor Xa inhibitor, it is of vital importance to administer the first

dose of heparin two hours before operation. If the heparin is given after the release of thromboplastin from traumatized tissue, the autocatalytic thrombogenic effect of thrombin will defeat the antithrombic effect of LDH.

Low-dose heparin is probably ineffective in major orthopaedic surgery and may not be used in conjunction with ophthalmologic surgery and neurosurgery.

To enhance the efficacy of LDH for the higher-risk groups, other methods have been devised, i.e. a dihydroergotamin mesylate-LDH combination, adjusted low-dose subcutaneous heparin, semisynthetic heparin analogue and low-molecular mass heparin.

Dextran

Dextran, a glucose polymer, lowers blood viscosity, decreases platelet aggregability and appears to render fibrin clots more susceptible to fibrinolysis.

Dextran 70 (mean molecular mass 70.000), which was developed as a plasma expander, remains in the intravascular space for a longer period than the smaller molecule dextran 40 (mean molecular mass 40.000). Dextran 40, which raises the oncotic pressure, draws fluid from the extracellular space, thereby improving the flow properties of blood.

The complications of dextran therapy include renal damage, abnormal oozing during operation, cardiac overload and anaphylaxis. An anaphylactoid reaction which has been reported in 0.4% of infusions may be avoided by the preadministration of a hapten. A recently developed agent, dextran I, is also said to reduce the incidence of reactions.

Berqvist has shown that after hip fracture surgery the incidence of DVT was significantly reduced by the combination of DHE and dextran 70 compared with dextran 70 alone. Fivew hundred millilitres of dextran 70 is infused twice on the day of the operation, once on days 1 and 3, and also on day 5 if the patient is still confined to bed.

The addition of graded compression with elastic stockings also increases the efficacy of dextran. Other prophylactic measures include ultra low-dose intravenous heparin, heparinoids (SP54), aspirin, ancrod and lidocaine.

Prothrombin Depressing Agents

Although it has been shown that oral anticoagulants are effective in preventing thrombosis after hip surgery or other high-risk procedures, the risk of peri-operative bleeding has limited their acceptance. The first really effective prophylaxis against postoperative deep vein thrombosis was pioneered by Sevitt and Galagher of the Birmingham Accident Hospital who showed conclusively that oral anticoagulants could significantly reduce the incidence of fatal pulmonary embolism after hip fractures from 18% in the control group to 2% in the treatment group. Although the incidence of bleeding complications was high, this was thought to be acceptable considering the potential lethality of the condition.

With adjusted low-dose warfarin therapy and the two-step approach in which a low-dose of the prothrombin depressing agent is administered several days before and continued

at a slightly higher dosage after operation, it has been shown that the incidence of thrombosis is significantly reduced without excessive risk of peri-operative bleeding.

Poller advised a therapeutic range for prophylaxis for DVT, including surgery, of a prothrombin ratio of approximately 2.0-3.0 (PT: 2-3 x normal). Poller believes that with strict laboratory control, oral anticoagulants could reduce the incidence of venous thromboembolism without jeopardizing haemostatic competence.

Non-Pharmacological Measures

Attention to Prevent Endothelial Damage

Prophylactic measures directed against the first of the Virchow triad, i.e. intimal damage, deserve consideration. Hypertonic solutions introduced into the veins of the lower extremities and pressure on the calf veins during operation should be avoided.

Venous stasis can be prevented by active ankle movement, early ambulation, intermittent pneumatic compression, electrical stimulation of the calf muscles and graded elastic compression stockings. Pressure exerted by the stocking should be graded at 18 mm Hg at the ankle, 14 mm Hg at mid calf, 10 mm Hg at the lower thigh and 8 mm Hg at the groin. TED (thromboembolism deterrent) stockings answer to this goal. Badly fitting stockings may have a tourniquet effect, are harmful and actually defeat the object.

Results of a recent analysis, the cost-effectiveness of alternative approaches to prophylaxis showed that the use of stockings is actually the only cost-saving prophylactic method. These results also suggested that LDH plus stockings and intermittent pneumatic compression plus stockings may substantially reduce the risk of venous thromboembolism, compared to single-agent prophylactic methods (such as heparin and stockings alone).

Resumé

The fundamental issue facing the surgeon is the selection of the **most appropriate** method of prevention in the individual case. This implies that adequate prophylaxis should probably be tailored to the risk involved in order to gain a maximum benefit-to-risk ration.

Nicolaides and Irving did a multivariate analysis study on 624 patients to assess the relationship between 14 clinical risk factors and the likelihood of postoperative venous thrombosis. A significant positive correlation was found between the development of thrombosis and five of these risk factors, i.e. the patient's age, the severity of surgery, the presence of varicose veins or infection at the time of surgery and premedication with Omnopon. A formula was devised to assess the risk of thrombosis in the individual case.

The calculated risk of thrombosis would for instance be 0.8% in a 20-year-old patient who has had minor surgery and 18% in a 60-year-old patient who has had major surgery. If there is a past history of venous thrombosis in the latter, the calculated risk would to 47%. The predicted risk of thrombosis in an 80-year-old patient with varicose veins and a past history of venous thromboembolism, who has had an operation involving an infected area, would be 96%.

Similarly, in 1976 Clayton *et al,* demonstrated that by using two laboratory tests and three clinical criteria, it was possible to design a prognostic index which gave good prediction of those at risk of developing postoperative deep-vein thrombosis. In this high-risk group the rate of deep-vein thrombosis was approximately 56%. With low-dose subcutaneous heparin prophylaxis given only to patients in the high-risk group, the incidence of deep-vein thrombosis was reduced to 6%. The possibility of identifying the high-risk group should therefore encourage a wider use of adequate prophylactic measures, where this group could be identified by means of a suitable predictive index.

If venous thromboembolism is a well-documented problem at the particular institution, prophylaxis should probably be offered to all patients over 40 years of age who require anaesthesia of more than 30 minutes duration.

For routine abdominal or thoracic operations the American Heart Association has recommended LDH therapy combined with graded compression stockings. For the higher risk group, adjusted low-dose heparin therapy may be considered with stockings or intermittent pneumatic compression. Where anticoagulants are contra-indicated, intermittent compression will probably suffice (eye surgery and neurosurgery).

Major orthopaedic surgery cases and the high-risk surgical case (hip surgery, the malignancies, previous venous thromboembolism or operation in an infected area, especially in the elderly) pose a special problem.

Although dextran, or a combination of LDH and DHE, and aspirin (for men) have been advocated, adjusted low-dose heparin for the intermediate risk orthopaedic group and mini-warfarin therapy or the "two-step" concept where warfarin therapy is commenced 10 to 14 days prior to surgery, appears to be worthy of support. Where warfarin therapy is contraindicated (patient with a prior pulmonary embolism and evidence of active duodenal ulceration) a transvenous umbrella filter should seriously be considered.

Patients with a mechanical heart valve (Star-Edwards, Bjork-Shiley or Saint Jude) are at serious risk with regard to intracardiac thrombosis. According to the guidelines laid down by the British Society for Haematology these patients are at maximum risk and require a therapeutic range with an international normalized prothrombin ration between 3.0 and 4.5.

Our own experience has shown that bleeding is rarely encountered during emergency or elective abdominal surgery in patients on well-controlled warfarin therapy, provided that the thromboelastogram shows reasonable haemostatic competence. Haemostatic breakdown associated with warfarin therapy is usually related to the effects of alcohol, aspirin, non-steroidal anti-inflammatory or other agents that the patient has knowingly or unknowingly taken. If for some reasons, i.e. pregnancy, warfarin is not acceptable in a patient with a mechanical valve, full heparinization should be considered. Low-dose heparin poses a grave risk of intracardiac thrombosis which requires emergency cardiopulmonary bypass.

Prophylaxis of Thromboembolism in Pregnancy

Pulmonary embolism remains the most common cause of pregnancy-related deaths in England and Wales.

Normal pregnancy is associated with several changes in the haemostatic mechanism. There is an increase in fibrinogen and factors VII, VIII and X, as well as a decline in plasminogen activator activity.

The progressive rise in hypercoagulability during the second half of pregnancy reaches a peak immediately after the third stage of labour and persists for approximately six weeks. The risk of fatal pulmonary embolism is now considered to be 16 times higher after caesarean section.

Although oral anticoagulant therapy has several drawbacks: possible teratogenic hazard during the first trimester, a risk of fetal haemorrhage and death if labour ensues while the patient is on oral anticoagulant therapy (prothrombin depressing agents are not excreted in the milk), heparin may safely be given as a prophylactic agent where there is a past history of venous embolism in the pregnant patient. Seven thousand five hundred units of subcutaneous calcium or sodium heparin are given 12-hourly during the first two trimesters. During the last trimester the dosage is increased to 10,000 units 12-hourly and continued for six weeks post-partum, with a brief period of cessation during labour. It should be noted that protamine causes marked uterine contraction.

Pregnant patients with mechanical heart valves are at grave risk of intracardiac thrombosis. Full heparinization is probably required during the first trimester and again four weeks before delivery. Oral anticoagulants may be given in the interim.

The Treatment of Established Venous Thromboembolism

The definitive treatment of venous thromboembolism includes anticoagulants, thrombolytic therapy and operative procedures to remove thrombus or embolus.

Anticoagulants

Heparin, probably the most reliable anticoagulant in use today, acts almost instantaneously. The anticoagulant action of heparin is mainly related to its antithrombin activity and to its ability to potentiate the inhibitory effect of antithrombin III (heparin co-factor) and the activated factors XIIa, XIa, IXa, Xa and thrombin (IIA).

Heparin does not cross the placenta and is not secreted in the milk. Although there is a risk of prematurity, it does not possess the teratogenic effects of warfarin. It is therefore the preferred form of anticoagulation of pregnancy. Bleeding as a result of heparin may be corrected with protamine sulphate on approximately a milligram basis (1 mg heparin = 100 units) given as a slow infusion not exceeding 5 mg per minute.

Although few would challenge the efficacy of heparin as an anticoagulant, worl opinion is still divided on the optimal dose, the route of administration and the laboratory

control.

Heparin may be given as a constant infusion, by intermittent - four- to six-hourly intravenous injections or eight- to twelve-hourly injections into the subcutaneous fat. However, it would seem that several influential authors favour continuous infusion in view of the fluctuation in heparin levels which occur with intermittent therapy. A useful formula is to give an intravenous bolus of 70 units per kilogram followed by a constant infusion of a 24-hour dose based on the formula:

(Body mass in kg x 100) / 2

This regimen is adjusted in order to maintain the APTT between 60 and 80 seconds, or one-and-a-half to two-and-a-half times the control value, or the Lee White clotting time between 20 and 30 minutes (N = less than 10 minutes). In the high-risk case (elderly patients especially females, other coagulopathy, recent aspirin or non-steroidal anti-inflammatory drug ingestion, hypertension, alcoholism, uraemia or recent surgery) extremely vigilant control is necessary. In these cases thromboelastography has been shown to be a most sensitive additional diagnostic parameter.

Heparin-induced thrombocytopenia is a serious complication of heparin therapy. Heparin should therefore not be considered in those patients where thrombocytopenia developed during previous therapy.

Heparin therapy is usually maintained for 10 days. The oral anticoagulant is commenced on day 5.

Oral Anticoagulants

Prothrombin-depressing agents act as competitive antagonists of vitamin K and interfere with the hepatic biosynthesis of prothrombin (factor II) and factors VII, IX and X. After the administration of an oral anticoagulant these factors disappear from the blood according to their turnover rates. Factor VII declines first followed by factor IX, factor X and prothrombin. Anticoagulation with coumarin compounds requires precise laboratory control. In view of the worldwide inconsistency in method, source of thromboplastin and interpretation of the results (prothrombin time, prothrombin index, prothrombin activity, prothrombin percentage), Biggs and her coworkers suggested a simple ratio (prothrombin time in seconds of the patient's plasma divided by the prothrombin time in seconds of a control plasma). Furthermore, the Manchester (human brain) thromboplastin has now become the standard reference against which each laboratory can compare results. A common system of reporting known as the international normalized ratio (INR) has now been laid down by the WHO. The proposed therapeutic guidelines of the British Society for Haematology are briefly summarized in table 1.

Table 1. Proposed ranges (British Society for Haematology, Guidelines on oral anticoagulants (1984))

British Ratio (INR)	Clinical state and usage
2.0-2.5	Prophylaxis of deep-vein thrombosis including high risk surgery.
	Prophylaxis for hip surgery and operations for fractured femur.
2.0-3.0	Treatment of deep-vein thrombosis, pulmonary embolism, transient ischaemic attacks.
3.0-4.5	Recurrent deep-vein thrombosis and pulmonary embolism; arterial disease including myocardial grafts; arterial grafts; cardiac prosthetic valves and grafts.

Bleeding as a result of coumarin or indanedione overdosage may be corrected by simple withdrawal or reduction in dosage, the administration of fresh whole blood, fresh frozen plasma or vitamin K.

Of the vitamin K preparations, phytomenadione (vitamine K1) is the most effective. If treatment with anticoagulants is to be continued, the smallest effective dose of phytomenadione should be given. Dosage should be controlled by PT determination at regular intervals. Mild cases of bleeding may be treated by the administration of a single dose of 1-5 mg. If bleeding is severe or life threatening, doses up to 25 mg, repeated after 8-12 hours may be indicated. However, it must be realized that large doses of the medication may render the patient refractory to anticoagulant therapy for periods of up to three weeks.

This may be extremely hazardous with mechanical heart valves where there is constant danger of embolization or intracardiac thrombosis. Patients with mechanical valves who present for elective or emergency surgery should continue with full oral anticoagulant therapy throughout the perioperative period provided the thromboelastogram shows reasonable haemostatic competence. Bleeding is rarely encountered if the patient is well controlled and is not taking aspirin or non-steroidal anti-inflammatory or other agents which are known to potentiate the action of the drug.

The duration of oral anticoagulant therapy must be individualized. Usually this varies from four to six months. However, if there are risk factors involved, i.e. cardiac failure, repeated thromboembolism, pulmonary hypertension, diabetes, obesity, postphlebitic limb, antithrombin III deficiency or defective fibrinolysis, this period may be extended indefinitely.

Thrombolytic Therapy

Fibrinolytic agents possess enzymatic activity that activate endogenous plasminogen (profibrinolysin) to plasmin (fibrinolysin). Urokinase and tissue plasminogen activator are derived from human sources and are therefore not antigenic like streptokinase which is derived from beta haemolytic streptococci. As streptokinase is a weak streptococcal antigen it is neutralized by circulating antibodies which may be present in high titre after previous streptococcal infections.

The loading dose recommended at present for streptokinase is 250000 units given over 30 minutes followed by 100000 units per hour for 24-72 hours.

The main disadvantage of urokinase is its prohibitive cost. However, in those cases with high-titre anti-SK antibodies where rapid lysis of thrombi is required, urokinase is an acceptable option. The recommended regimen for UK is 4400 IU per kilogram given over 10 minutes every hour for 12-24 hours. On conclusion of a course of the thrombolytic agent, heparin therapy is commenced as soon as the TT or PTT is less than twice the control value.

The laboratory tests which may be applied to assess the efficacy of the thrombolytic programme are the following: PT, PTT, TT, FDP and euglobin lysis time.

The TT, probably the most widely used, is a sensitive indicator of the fibrinogen levels and the presence of FDPs. The TT is also sensitive to heparin therapy. Unfortunately these tests have limited value as predictors of haemorrhage. When this occurs immediate cessation of therapy is indicated. Antifibrinolytics should be close at hand in case of severe haemostatic breakdown which does not respond to fresh frozen plasma.

The contraindications to thrombolytic therapy include abdominal or thoracic surgery, other coagulation defects, severe hypertension, recent cerebro-vascular accident, active tuberculosis and visceral and intracranial malignancy.

Tissue plasminogen activator (tPA), a recent development, may prove to be a major advance in view of its propensity to evoke lysis at the site of fibrin formation without causing systematic hyperplasminaemia. However, at present costs are too prohibitive for general use.

Surgical Management of Thromboembolism

Thrombectomy

Although thrombectomy has been advocated for several decades, it seems that thrombus removal does not affect early morbidity or the late sequelae of the post-phlebitic limb. Extensive thrombosis in the collateral circulation and recurrence appear to be the major drawbacks after operative removal. Therefore iliofemoral venous thrombectomy is usually reserved for patients with àphlegmasia caerulea dolensà with a threatened limb or a recent ßÑ ive right iliofemoral venous thrombosis where there is a serious risk of fatal embolism. Thrombectomy should be followed by anticoagulation. Hypercoagulability as a result of some underlying inflammatory, neoplastic or metabolic disease should always be excluded in all cases of àphlegmasia ßÑ olens.

Venous Interruption

Interruption of the inferior vena cava for the prevention of pulmonary emboli has now been simplified by the use of transvenous catheter devices placed under local anaesthesia. These include the Kimway-Greenfield filter, Eichelter sieve, Hunter balloon and the Mobin-Udine umbrella.

In patients with proximal deep-vein thromobosis of the lower limb, the indications for caval interruption include the following:

- recurrent pulmonary emboli despite adequately controlled anticoagulant therapy

- conta-indication to anticoagulants

- cessation of treatment owing to complications of anticoagulant therapy

- septic thromboemboli despite adequate antibiotic therapy

- pulmonary hypertension as a result of chronic recurrent pulmonary emboli. Caval interruption is also indicated at the conclusion of pulmonary embolectomy.

Pulmonary Embolism

Despite the fact that pulmonary embolism is the third most frequent cause of death in the USA, the diagnosis is missed in 70-80% of cases. Furthermore, Barritt and Jordan have shown that when a patient has a pulmonary embolism, anticoagulant therapy reduces the risk of death from that embolism. The likelihood of recurrent embolism is also diminished. It would seem that timely therapy based on a high index of suspicion, as well as an aggressive diagnostic ritual, is of fundamental clinical importance.

Diagnosis

The clinical picture of pulmonary embolism may vary from minimal symptoms to sudden death.

The symptoms in order of frequency are dyspnoea (81%), pleural pain (72%), cough (54%), apprehension (39%), and haemoptysis (34%).

Similarly the signs are tachypnoea (87%), rales (53%), accentuated second pulmonary sound (53%), tachycardia (44%), fever (42%), S3 and S4 gallop sounds (34%) and sweating (34%).

Special Investigations

Laboratory tests are also nonspecific. The classical triad of raised serum LDH, SGOT and bilirubin has not come up to expectations.

Similarly the main advantage of the electrocardiogram seems to exclude myocardial

infarction. The chest X-ray may show consolidation, an elevated diaphragm, pleural effusion, prominent pulmonary vasculature, atelectasis, focal oligaemia or right ventricular strain.

The measurement of the arterial oxygen tension is currently one of the most useful tests. Greenfield proposed that the diagnosis of pulmonary embolism is most likely in the hypoxaemic patient who is hypobaric ($PaCO_2$ less than 30 torr) and has tachycardia (heart rate greater than 100 per minute).

Multiple-view perfusion lung scanning combined with radionuclide venography is considered to be the most useful screening test for pulmonary embolism. Although sensitive, its specificity is affected by other cardiorespiratory conditions and the test should therefore be interpreted in conjunction with a chest X-ray and preferably a ventilation study. Sassahara et al. have stressed the importance of the site of thrombus formation as the source and therefore a valuable aid in the diagnosis of pulmonary angiography and electrical impedance plethysmography. If the impedance plethysmogram is normal, the likelihood of pulmonary embolism is less than 10%. However, the definitive diagnosis, especially in cases with a history of previous cardiopulmonary disease, is established by selective pulmonary arteriography.

Management

Well-controlled anticoagulant therapy remains the cornerstone of treatment of venous thromboembolism. Heparin acts immediately by inhibiting both pathways of blood coagulation, preventing clot propagation and blocking the release of vasoactive and bronchoconstrictor substances which are released by blood platelets. Heparin should be administered as soon as a major embolism is suspected in order to minimize the possibility of the propagation of the embolus or a second embolic episode. Seven thousand five hundred units should be given as a intravenous "covering" dose in order to achieve anticoagulation during the diagnostic workup. As soon as the diagnosis is established, full heparing therapy by constant infusion is commenced.

Although thrombolytic therapy seems to be a rational approach, the urokinase pulmonary embolism trial showed that, although clot dissolution was significantly accelerated, there was no difference in the mortality or lung haemodynamics (at six months and one year) in those treated with urokinase. This trial also indicated that there was an increased risk of haemorrhage with the use of thrombolytic agents. However, a case can be made for those patients with massive embolism who do not qualify for embolectomy.

Embolectomy

Open pulmonary embolectomy, which is indicated in fewer than 10% of cvases, should be considered where intensive measures, including vasopressors, oxygen and heparin therapy fail to evoke a satisfactory response after one to two hours. In cases of massive embolism the patient is taken to the operating suite for partial cardiopulmonary bypass by cannulation of the femoral artery and vein under local anaesthesia. If the patient qualifies for embolectomy, partial bypass may be converted to total bypass after general anaesthesia followed by sternotomy.

Transjugular or femoral venous embolectomy by means of suction catheter as proposed by Greenfield may be conducted under local anaesthesia and under fluoroscopic control. This ingenious method is, however, less likely to be effective after 72 hours and where there is more than 50% occlusion of the pulmonary artery.

Comment

Venous Thromboembolism

A. du P. Heyns

Several important questions must be considered by the clinician who is faced with this common and important disease:

- Does the patient really have venous thromboembolism?

- Is the proposed anticoagulant therapy of benefit to the patient with deep venous thrombosis or pulmonary thromboembolic disease?

- How long should heparin and warfarin therapy be continued?

The major problem with evaluating the efficacy of therapy is that in only about one-third of patients with symptoms and signs suggestive of deep venous thrombosis or pulmonary thromboembolism, is the diagnosis confirmed with a wholly satisfactory technique (venography or pulmonary angiography are the "gold standards"), despite universal recognition that a clinical diagnosis is unreliable. The common practice to treat with anticoagulants solely on the basis of clinical features has the important aftermaths that many patients are treated unnecessarily at considerable expense and inconvenience, and are exposed to the hazard of one of the leading causes of drug-induced disease and death.

Despite the results of many published studies, and the use of anticoagulants for half a century, it is still not unequivocally clear whether anticoagulant therapy is beneficial for deep venous thrombosis and pulmonary thromboembolism. This is because no placebo controlled randomized trials with objective criteria for the inclusion of patients and establishing the end point of therapy, have been reported.

There is no consensus on the optimal duration of heparin therapy. In the USA prolonged heparin therapy for seven to fourteen days is the rule although there is no conclusive proof that this expensive approach is warranted. In the UK heparin is usually given only until oral anticoagulants, started simultaneously, have prolonged the prothrombin time ration within the therapeutic range. There is evidence that such a shorter course of heparin therapy is as effective as the American practice.

An important question relates to the optimal duration of oral anticoagulant therapy. Although common practice is to continue for six months, the unreliability of clinical diagnosis makes the trials on which this regimen is based of little value. Based on the results of acceptable randomized trials, it is recommended to administer oral anticoagulants for siw weeks to three months in patients with proven deep venous thrombosis, and for three to six

months for those with proven pulmonary thromboembolism with no complications.

The standardization of the prothrombin ratio and reporting the results as an INR (international normalized ratio) has already done muct to standardize anticoagulant therapy. At present it is recommended to maintain the INR within the therapeutic range of 2.0 and 3.0. This should substantially reduce the high risk of bleeding associated with warfarin previously reported, especially in America. It has now become obvious that these patients had been relatively overtreated because of the lack of sensitivity of the thromboplastin used for the laboratory control of anticoagulant therapy.

Although the management of venous thromboembolism remains problematical, a considered effort to always base the diagnosis on the results of objective tests, the continued evaluation and search for optimal treatment schedules, and the standardization of laboratory control of oral anticoagulants should in due course resolve many of these problems.

Comment

Venous Thrombosis and Pulmonary Embolism

E. J. Immelman

In the preceding chapter a balanced and up to date resume of the aetiology, prevalence, diagnosis, treatment and prophylaxis of venous thromboembolism is given.

The area of greatest controversy at present revolves around the question of prophylaxis in surgical patients. A recent statistical analysis of all low-dose heparin (LDH) studies by Collins and his colleagues provided compelling evidence that LDH used in a dose of 5000 u either eight or 12-hourly postoperatively reduced the risk of pulmonary embolism (PE) by plus minus 50% and deep-vein thrombosis (DVT) by plus minus 60% in general surgical, urological, gynaecological and orthopaedic surgery. However, the risk of bleeding in patients receiving LDH is increased.

The publication of this paper, together with the National Institute of Health Consensus Statement stressed the medico-legal implications of not employing prophylaxis where this is indicated. Recent international surveys amongst general and orthopaedic surgeons revealed that only a minority routinely employ prophylaxis in patients over the age of 40 years undergoing major surgery. The reluctance of surgeons to employ prophylaxis routinely is based on a fear of side-effects and the question of benefit-to-risk. This dilemma can best be illustrated by examining the logistics of prophylaxis in major general surgical procedures in patients over 40. Assuming that the contemporary incidence of fatal PE is in the order of 0.5% in this category of surgery, the routine use of LDH in 1000 patients could result in the saving of two or three lives. As a significant proportion of fatal PE occur in patients with end-stage cardio-respiratory disease of metastatic carcinoma, the net saving in patients who would otherwise have recovered, may be as low as one or two patients. The remaining 996 patients would have received largely unnecessary prophylaxis. If prophylaxis were inexpensive, easily applied and devoid of side-effects such a policy would be justified. Side-effects, however, remain a matter of concern even if their incidence is low. These include bleeding complications with oral anticoagulants and LDH, vascular overload and anaphylaxis

with dextran and ischaemic complications when heparing is combined with dihydroergotamine. In a recent survey the syndrome of autoimmune heparin-induced thrombocytopenia, previously thought to be rare, has been shown to occur in 0.6-10% of patients exposed to heparin. This syndrome is associated with significant morbidity and mortality rates of 12-23%. Therefore in the minds of many surgeons the benefit-to-risk equation of the *routine* use of pharmacological prophylaxis remains unresolved.

Based on contemporary knowledge, the following scheme is offered as a guide:

1. Absolute indications for prophylaxis

A. *Patient with congenital deificiency requiring SX*

i *Anti-thrombin III (Heparin ineffective)*

Prophylactic warfarin with ATIII concentrates

ii *Protein C or S:* LDH prophylaxis plus protein C or S concentrates if available

B. *All patients on oestrogens* (Oral contraceptives or therapy)

Whatever age and however minor the surgery (i.e. appendicectomy) should receive LDH

2. Highest risk

Orthopaedic surgery

Hip fractures Hip replacement Knee replacement	DVT 50-80% Fatal PE 1-5%	Dextran - or 2 step warfarin - or adjust dose heparin - or heparin plus DHE - or LDH plus stockings

3. Highest risk

Abdominal surgery

General, gynecological Urological, Age > 40 plus additional risk	DVT 30% Fatal PE 0.8%	LDH - or low molecular heparin - or LDH/DHE - or LDH, compression and stockings - or dextran

4. Moderate risk

Major abd surgery Age > 40 No other risk factors	DVT 10-20% Fatal PE 0.1-0.2%	Pneumatic compression and plus stockings - or Nil

5. Low risk

Age < 40 Major or minor surgery no risk factors	DVT 10% Fatal PE 0.01%	Nil or stockings

Physical methods of prophylaxis are attractive because they are devoid of side-effects. Intermittent sequential compression of the legs during operation and the post-operative wearing of well-fitting, graduated compression stockings have both been shown in randomized studies to significantly reduce the incidence of DVT. The use of predictive formulae and the estimation of risk factors can provide a rough guide of the patient at greater risk. Risk factors with highest prediction include venous thromboembolism within the preceding year, major surgery within three months, congenital coagulation factor deficiency syndromes and patients taking oestrogens. Moderately predictive risk factors include obesity, sepsis, malignant disease and age.

Note: The risk of fatal PE after neurosurgical procedures is not known. Because even a small intracranial or intraspinal bleed may be catastrophic, dextran, warfarin or LDH should *not* be used. Consensus favours intermittent pneumatic compression plus stockings.

Chapter 3.12: Fat Embolism and the Fat Embolism Syndrome

B. G. P. Lindeque

Introduction

The early history of fat embolism was recounted by Weisz (1974) and refers to the first report by Lower of Oxford (1669) who injected milk intravenously into experimental animals and found fat globules in the pulmonary vessels at autopsy. Weisz attributed the first histological proven case of fat embolism to Zenker (1862) in a patient who died after a severe crush injury.

In the early 1950s Peltier's studies expanded our knowledge of the pathogenesis and he noted the toxic effects of free fatty acids. The result was a description of the respiratory theory which is still valid; it is the basis of current therapeutic regimens. Much confusion still exists in the nomenclature as far as the fat embolism and shock lung syndromes are concerned. In this chapter an effort will be made to clarify the concepts of fat embolism, the fat embolism syndrome and the shock lung syndrome (ARDS).

Definitions

- The term "fat embolism" denotes the presence of globules of fat in the lung parenchyma and peripheral circulation after a fracture of long bone or other major trauma;

the complication arises in the vast majority of such cases (more than 90%).

- The term "fat embolism syndrome" (FES) denotes a serious manifestation of fat embolism which gives rise to a clinico-pathological shock lung syndrome. The incidence of the fat embolism syndrome is nevertheless 29% in out experience depending on the criteria for a positive diagnosis (see below). The fat embolism syndrome is a respiratory deficiency syndrome due to decreased alveolar diffusion of oxygen. It occurs in three degrees of severity, i.e. a subclinical, an overt clinical and a fulminating form. The latter fulminating form is frequently fatal, while the subclinical and clinical forms are more amenable to treatment. The shock lung syndrome (adult respiratory distress syndrome) is a more widely used term which describes an insult to the respiratory system as well and therefore also leads to decreased alveolar diffusion of oxygen. However, ARDS may be caused by different patho-physiological mechanisms, i.e. the inhalation of toxic gases, hypovolaemic shock, septicaemia, and lung contusion. The advantage of the term "fat embolism syndrome" is its specificity in denoting the shock lung syndrome due to long-bone fractures. The term fat embolism syndrome, therefore, should be used only to describe the adult respiratory distress syndrome due to long-bone fractures. If concomitant injuries are present in a patient with a long-bone fracture, i.e. lung contusion, rib fractures or cerebral trauma, the term adult respiratory distress syndrome (ARDS) should be used instead of "fat embolism syndrome" (FES).

Bone

Fat globules diametrically larger than 10 to 20 micronmetres are driven into the wide non-collapsible veins of the Haversian canals due to high tissue pressure during trauma. The fat macroglobules appear in the bloodstream and are trapped in the lung capillary network. The fat globules are usually too large to escape from the lung capillary system; they lodge themselves in the lung capillaries and cause mechanical obstruction.

Blood

Fat macroglobules may also appear inthe bloodstream due to the release of stress hormones, i.e. adrenaline, glucagon, glucocorticoids and growth hormone, which enhances lipid instability in the circulation.

Trauma leads to the release of tissue thromboplastin as well which activates the platelets present in normal blood. Platelets adhere to collagen surfaces (especially damaged collagen surfaces in the region of the fracture) as well as on the fat globules. Platelets then release vaso-active amines, i.e. serotonin which causes bronchospasm and vasospasm. Platelet aggregation also enhances the reactions of factor IX with factor VIII and factor X, with factor V with an increased risk for the development of a consumption coagulopathy. A full-blown DIC may ensue. Stress hormones increase free fatty acids, triglycerides, cholesterol and chylomicrons in the blood. The free fatty acids, especially oleic acid, cause chemical inflammation of the lung capillaries. The unbound fraction of the free fatty acids is further increased due to the lowered plasma albumin value caused by haemorrhage. Only 1% of free fatty acids is physiologically not bound to albumin. In shock the unbound level of free fatty acids increases as a direct consequence of the decrease in the albumin concentration. This leads to an abnormal concentration of unbound free fatty acids which adhere to the fat macroglobules in the lung, and cause chemical damage to the capillary endothelial cells of

the lung. There is a definite double effect of blood lipid changes: fat macroglobules obstruct the lung capillary system mechanically and free fatty acids cause chemical damage to the capillary endothelial membrane, thus increasing the permeability of the capillary endothelial membranes.

Lungs

The lung capillaries act as a filter for most emboli. However, a proportion of the emboli reaches the systematic circulation via the so-called A-V shunts in the lung, or due to amoeboid movement of macroglobules through the lung capillaries, or as a consequence of fat droplet coalescence in the systemic circulation after passing through the lungs.

The shock lung syndrome is a direct consequence of the mechanical and chemical effects of the lipids on the lung capillaries. Mechanical blockage causes an increased resistance to blood flow, increased pulmonary arterial pressure, increased righ ventricular load as well as perfusion disturbance which results in an increased shunt and ventilation-perfusion imbalance. In the fulminating form of FES, the mechanical capillary obstruction is of such magnitude that it is usually beyond treatment. The chemical effects on the lung are due to free fatty acids, especially oleic acid which damages the lung capillaries. It may also be due to the breakdown of fat macroglobules to glycerol and free fatty acids in the lung capillaries, the damage done by vaso-active amines, i.e. serotonin, the release of hydrogen peroxide, super oxides, acid phosphatase, catepsins and a permeability factor released by the platelets. The dominant factor amongst these that lead to the FES is not known. The chemical effects on the lung capillaries lead to an increased diameter in the interendothelial phase, increased capillary endothelial permeability, interstitial oedema, increased alveolar capillary diffusion distance and an accumulation of transudate in the alveoli. This is followed by an accumulation of exudate in the alveoli, death of the type II pneumocytes and decreased production of surfactant. Congestive micro-atelectasis, accumulation of red blood cells in the alveoli and decreased lung compliance ensues. This leads to an increased workload on breathing, an increased shunt and increased ventilation-perfusion disturbance in both lungs.

Systemic Circulation

Fat emboli escaping from the lung circulation break up into glycerol and free fatty acids due to lipase activity present in tissues. The free fatty acids lower capillary endothelial adhesiveness which leads to increased permeability and the escape of fluid and red blood cells from the circulation (possibly the reason for petechiae). The following organs are involved:

- Brain: two mechanisms cause symptoms:

  - cerebral hypoxaemia is caused by the generalized hypoxaemia and by the fat macroglobules which obstruct the small cerebral capillaries and

  - free fatty acids which damage brain capillaries. This leads to petechiae, interstitial oedema and cerebral hypoxaemia.

- Eye: Emboli are observed on the retina which may reach the retinal vessels. Bleeding and exudates ensues. Petechiae are visible in the sclera and conjunctiva.

- Skin: Petechiae are usually visible on the chest, the axilla and on the neck. Petechiae usually subsides after 24 to 48 hours. One should, however, note the fact that only a small percentage of people with the overt fat embolism syndrome develop petechiae for a long time. Petechiae should therefore not be considered an important factor in the diagnosis of the fat embolism syndrome.

- Urine: Fat droplets are occasionally visible in urine as well as in sputum.

Clinical Signs

It is important to note that initially no clinical symptom or sign may be apparent. A patient may suffer the subclinical form of the fat emolism syndrome which is only realized when a blood gas analysis is performed. It is therefore of the utmost importance not to wait for overt clinical symptoms and signs before the diagnosis of the fat embolism syndrome is made. If the over clinical symptoms and signs are present the following are noted:

Respiratory Signs

Tachypnoea, dyspnoea, increased workload on breathing or bronchi and crepitations.

Cerebral Signs

Delirium, confusion, disorientation, aggressiveness, irritation and coma may ensue. In rare instances diabetes insipidus may develop as well. Hyperpyrexia may be present as well as central cyanosis.

Skin

Petechial rash is present. Retinal changes may be seen: fat emboli, bleeding and exudates are sometimes seen in the retinal vessels. Fat droplets in the urine and sputum may be present as well as widespread DIC.

Cardiovascular Signs

A tachycardia between 120 and 140 per minute, mild hypotension and decreased pulse pressure are present.

None of the above symptoms and signs are diagnostic of the fat embolism syndrome. The diagnosis of the fat embolism syndrome may be made with confidence only if one adheres to the principles laid out in the next section (vide infra).

Diagnosis and Special Investigations

No clinical sign or symptom is pathognomonic of the fat embolism syndrome: reliance on overt clinical symptoms and signs will delay the diagnosis and early treatment. ARDS due to the fat embolism syndrome is at times not distinguishable from ARDS caused by shock and trauma. It is therefore extremely important that a high index of suspicion be maintained after every injury and early diagnosis be made not only by symptoms and signs but by doing a

vital blood-gas analysis. Most cases of the fat embolism syndrome present after a period of 24 to 72 hours after injury. Haemodynamic shock is usually present with the fat embolism syndrome. Shock contributes to the development of ARDS. Certain risk factors have been identified which contribute to the development of the fat embolism syndrome. They include:

- high-velocity injuries (motor vehicle accidents)

- the degree of shock

- the duration of shock

- fractures not immobilized prior to transportation

- patients transported by aircraft over long distances

- concomitant conditions, i.e. sepsis, lung contusion, thoracic injuries, aspiration of solids or fluids, head injuries and multiple blood transfusions through a standard blood filter.

The differential diagnosis of the fat embolism syndrome include:

- aspiration pneumonia

- lung contusion

- over-transfusion

- pneumothorax

- diffuse bronchopneumonia

- other causes of ARDS.

Blood-gas analysis is mandatory in the diagnosis and treatment of the fat embolism syndrome. Most important on the blood-gas values is a lowered PvO_2 (mixed venous oxygen concentration obtained through a pulmonary artery catheter). While most of the patients are not admitted into an intensive care unit where a Swan-Ganz catheter is passed, this investigation is done in the severely injured and shocked patients only. Therefore an ordinary blood-gas analysis is the prime investigation in most of the patients. A lowered PaO_2 may be seen which later rises to above normal. In our experience the $PaCO_2$ is not as valuable as the PaO_2 in the diagnosis of the fat embolism syndrome. An initial respiratory alcalosis and metabolic acidosis may be followed by a respiratory acidosis and metabolic acidosis, as the disease proceeds.

If serum urea, electrolytes and protein values are done, one usually finds a low plasma albumin, a high plasma FFA (free fatty acids - unbound fraction), a low haematocrit and haemoglobin. We were unable to demonstrate a constant thrmobocytopenia in patients with a fat embolism syndrome.

Blood hypercoagulability is occasionally seen as well as ECG changes in the form of right ventricular strain. X-ray changes (present in only30% of the cases) is a late phenomenon, they include: a loss of normal lung vascular pattern, sometimes a bilateral snow-storm appearance in the severe cases or even the so-called white lung syndrome. The blood gas values are critical but the X-ray picture may be confusing and does not correlate with the severity of the patient's condition. It is incorrect to wait for an absolute drop in the PaO_2 to 60 mm Hg before the diagnosis of the FES is made. If a patient's initial PaO_2 is 90 mm Hg and it drops steadily with consecutive PaO_2 determinations, it is not necessary to wait for the PaO_2 to drop to below 60 mm Hg before the diagnosis of the fat embolism syndrome is made. This patient has most probably developed the fat embolism syndrome and treatment should be administered promptly.

Treatment

Prophylacis of the clinical form of the fat embolism syndrome is the best treatment. The severe form of the fat embolism syndrome may be prevented by maintaining a high index of suspicion and by treating patients in the *early* phase of the disease. Shock must be treated early and aggressively. Fractures should be splinted *adequately*. This is especially imortant if a patient is transported by ambulance or even by aircraft over long distances. One should prevent the aspiration of fluids and solids especially in comatose and semicomatose patients. It is also important to fit a nasogastric tube in patients with multiple fractures or fractures of the pelvis. These patients suffer so much pain that they are unable to move and they would rather aspirate vomitus than turning on their side to expel the vomitus. One should prevent sepsis by aggressively debriding open fractures. Multiple blood transfusions should be administered through a special microfilter. Oxygen should be administered by mask if the PaO_2 level is less than 70 mm Hg. Please note: it is not necessary to wait for the PaO_2 to drop below 70 mm Hg before administering oxygen, if one is able to prove a steady drop in the PaO_2 in a patient before it reaches the level of 70 mm Hg. At the same time one should encourage aggressive lung physiotherapy.

We have proved the efficacy of Methyl-prednisolone (Solu Medrol) administration at a dose of 30 mg/kg immediately on admission as well as once after four hours without doubt. In a double blind-controlled prospective randomized study, Solu Medrol was proved to be efficacious above the placebo group. Our research has been verified by others. It has now been established that early administration of intravenous methylprednisolone leads to higher PaO_2 values in patients with long-bone fractures. We therefore encourage physicians to administer methylprednisolone in the dose prescribed above. Please note that Solu Medrol is not a "wonder" drug. It is detrimental therefore to rely on the administration of Solu Medrol and omit all the other prophylactic measures. Methylprednisolone will be advantageous only if the treating physician adheres to all the prophylactic measures in the treatment of patients with the fat embolism syndrome. The indications for ventilatory support in our unit is as follows:

- a PaO_2 less than 60 mm Hg in spite of an oxygen mask

- a PCO_2 of more than 50 mm Hg

- a respiratory rate of more than 55 per minute

- a pH of less than 7.3 or laboured breathing.

If one of these factors is present, even after adequate sedation, ventilatory support should be instituted. The type of ventilatory support is CPAP or IMV. The aim of ventilatory support is to maintain adequate tissue oxygenation.

Prognosis

The prognosis of the fat embolism syndrome is related to the effectiveness of preventative measures and early detection, therefore one should diligently apply these measures and treat patients early for the fat embolism syndrome. If one adheres to the above principles, only a very small percentage of patients will reach the stage where ventilatory support in the form of mechanical ventilation will be necessary. It is in the patient's best interest to prevent the protracted form of the fat embolism syndrome by adhering to the above-mentioned principles.

Comment

Fat Embolism

K D Boffard

In the traumatized patient, respiratory problems are one of the greatest causes of morbidity. Aggressive prophylaxis forms the single best weapon in the management of these patients, especially on the Highveld where the clinical presentation of fat embolism syndrome is double that at the coast.

Oxygenation

Adequate oxygenation is essential. Just because a patient is not "blue" does not mean that he is not hypoxic. Following trauma, there is capillary shutdown and sludging of red cells, and although central oxygenation is adequate, tissue perfusion may be poor. One hundred per cent oxygen, by whatever means (mask, nasotracheal tube, etc), should be administered at least until resuscitation is complete.

Early Fluid Resuscitation

Early resuscitation is essential and ideally should be complete, with the circulation stable no more than 60 minutes after injury - the concept of the "golden hour".

Resuscitation should take advantage of the fact that the best haematocrit for body efficiency is a PCV of 30%, equivalent to a haemoglobin of 10 g/dL. This is the best compromise between haemoglobin and viscosity. A fall of the haemoglobin below this level results in an increasingly dramatic fall in oxygen saturation, and is to be avoided if at all possible. The net result is that any blood loss of less than approximately 2 litres may be replaced with crystalloid or colloid, but thereafter replacement with blood, preferably fresh, is essential.

Crystalloid Restriction

Patients should be restricted to a maximum of 1 litre of crystalloid (commonly Ringers Lactate). This is because of their short halflife of 20 minutes in the circulation. Colloids should be used early. Dextran 70 in a dose of 5-10 mL/kg body weight not only holds crystalloid in solution by virtue of its hyperosmolar effect, but additionally has a specific effect of preventing rouleaux formation with an improvement in tissue perfusion. Synthetic plasma derivatives such as Haemaccel should be used instead of dried plasma, both for cost reasons and in view of current problems with AIDS.

Early Immobilization of Fractures

This has dramatically improved the results, and early splinting by paramedics at the roadside followed by early reduction and fixation in hospital has contributed much.

Steroids

The use of steroids remains controversial. While there is no doubt that methylprednisolone will result in an improvement of the incidence of fat embolism syndrome, all steroids have an effect on the immune system. A single dose of methylprednisolone can immunosuppress a patient for a week. Therefore the advantage of their use in FES must be balanced against the disadvantage of increased risk of sepsis, especially wound sepsis, and pneumonia, including a full picture of ARDS.

Chapter 3.13: Acute Renal Failure (ARF) in the Surgical Patient

D. J. du Plessis

Introduction

Acute renal failure (ARF) is a potentially fatal condition in the patient following trauma or surgery. Many patients are exposed to a large group of nephrotoxic substances and contrast media, blood transfusions, antibiotics, anaesthetics, and pre-operative and post-operative medications may also be contributing factors. Renal dysfunction in this group coincides with an accelerated catabolic rate with a rapid increase in blood urea. Immediate and effective diagnosis and management of each component of the multifactorial aetiology of acute renal dysfunction (ARF) may prevent a train of events. This offers the acutely ill patient the best chance of surviving this frequently fatal disease.

Definition

ARF is a potentially reversible clinical syndrome presenting with a sudden decline in glomerular filtration rate (GFR), which leads to an increase in blood urea and serum creatinine levels. The focus of the clinician should be on the urine quality rather than quantity because non-oliguric forms of ARF exist. ARF is usually manifested by oliguria, or sometimes anuria, but high output renal failure (polyuria) also occurs.

Oliguria is a urine volume less than 500 mL/day or 20 mL/hour which is an

insufficient urine volume to excrete products of the metabolism.

Non-oliguria (high-output renal failure) is a urine volume above 2000 mL/24 hours.

Anuria is a urine volume between zero and 50 mL/24 hours due to post renal obstruction or severe parenchymal disease (acute tubular necrosis of renal cortical disease).

Aetiology and Classification

When the surgeon is confronted with the problem of an abnormal decrease or increase in urine output or abnormal blood indices indicating uraemia, the search for aetiological factors should be started immediately. The classification of the causes of ARF into prerenal, renal and postrenal remains a useful and logical approach.

Prerenal Failure

The kidney function is normal but an abnormally low organ perfusion exists. This results in a decreased filtration pressure with subsequent oliguria. The causes of haemodynamic alteration in kidney perfusion are hypovolaemia, hypotension (renal vasoconstriction) and myocardial pump failure.

Hypovolaemia (Decreased Effective Arterial Blood Volume)

- Intravascular volume loss

1. Blood loss

2. Plasma loss (burns)

- Extravascular volume loss

1. Vomiting (bowel obstruction)

2. Diarrhoea (ulcerative colitis)

3. Diabetes insipidus (head injury)

- Fluid shift from intravascular to extravascular spaces

1. Ascites

2. Peritonitis

3. Pancreatitis

Hypotension (Renal Vasoconstriction)

- Sepsis (septic shock)

- Anaphylaxis (penicillin sensitivity)

- Medications (ganglionic blockade)

Myocardial Pump Failure

- Congestive heart failure

- Massive pulmonary embolism

- Pericardial tamponade

The importance of prerenal failure lies in its potential reversibility if diagnosed and managed actively initially.

Renal Failure

This results from all conditions that damage the renal parenchyma, with subsequent abnormal urine production and excretion. The possible causes are:

Acute Tubular Necrosis or Vasomotor Nephropathy (ATN)

When systemic circulatory impairment is severe and prolonged correction of the systemic circulatory dynamics does not restore normal renal function. This is because of the development of renal parenchymal damage and transition to ATN.

/- Surgical hemorrhage

/- Ischaemia

/- Infection (gram negative sepsis)

/- Progression from prerenal and postrenal failure

/- Nephrotoxins

- Drugs and dyes

- Anaesthetics

- Haemoglobinuria (incompatible blood transfusion)

- Myoglobinuria ("crush" injuries)

- Snake venom

/- Disseminated intravascular coagulation

- Snake venom.

Glomerular Disease

- Various glomerulonephritides

- Vasculitis

- Nephropathies

Postrenal Failure

This accounts for 10% of all patients with decreased renal function. Outflow obstruction of urine distal to the functioning nephron should be suspected in patients with oliguric or non-oliguric ARF. It may lead to parenchymal damage and progress to intrinsic (established) ARF. The causes are:

Mechanical Obstruction

/- Lower urinary tract, i.e. urethral obstruction (distal to bladder neck)

- Posterior urethral valves

- Benign or malignant prostatic enlargement

- Urethral stones or clots

- Occluded indwelling catheter

- Urethral strictures

/- Mid-urinary tract, i.e. bladder

- Bladder stone

- Bladder tumours

- Atonic bladder due to autonomic neuropathy and spinal cord lesions

/- Upper urinary tract, i.e. ureters

- Surgical ligation of ureters during hysterectomy or colectomy

- Bilateral ureteric calculi

- Unilateral ureteric stone with reflex anuria

- Retroperitoneal fibrosis

- Retroperitoneal malignancy.

Functional Obstruction

This is due sphincter or drug induced spasm secondary to anticholinergic or narcotic medications.

Surgical Anatomy

The kidneys are situated in the retroperitoneal space and supplied by a single renal and/or accessory artery at the level of the first lumbar vertebra. After entering the renal substance it divides into interlobar arteries along the medullary pyramids. The interlobar arteries form the arcuate arteries at the base of the renal medulla.

The interlobar arteries branch from the arcuate arteries and extend to the periphery of the renal cortex.

The afferent arteriole, a branch of the interlobular arteries, supply each glomerulus with oxygenated blood. The glomerular capillaries, the first capillary bed, rejoin to form the efferent arteriole which branches to form a secondary capillary bed (peritubular capillary bed) surrounding the distal tubuli. They coalesce to form venules and ultimately the renal veins. The afferent and efferent arterioles are extremely active resistance vessels which autoregulate the renal blood flow and glomerular filtration rate (GFR).

This anatomic arrangement of the nephron forms the foundation of out modern knowledge of kidney function and acute ischaemic tubular necrosis.

Kidney Functions

The kidney functions are:

- The maintenance of extracellular fluid (ECF) volume

- Ionic concentration

- Excretion of the metabolic nitrogenous waste products

Extracellular Fluid Volume and Concentration

This is maintained by reabsporption of most of the glomerular filtrate (fluid, sodium, chloride, potassium, calcium, bicarbonate, phosphate, glucose, amino acids and other solutes) by the proximal tubule. In the distal tubule active modulation of the remaining tubular fluid takes place. It is here that sodium, potassium and acid secretion is regulated by the adrenal hormone aldosterone. Water is excreted secndarily, or conserved. For these normal regulatory

functions to operate the following are mandatory:

- Sufficient glomerular bloodflow and filtration pressure.

- Structurally and functionally normal tubules.

- Normal flow of fluid throughout the nephron.

- An intact peritubular circulation.

Abnormality in any of these factors may lead to nephron dysfunction and a disturbance of the milieu interieur.

Metabolic Nitrogenous Waste Products

The excretion of metabolic nitrogenous waste products depends on an intact glomerular bloodflow and filtration. The excretion of urea in the urine depends entirely on the GRF and flowrate of filtrate through the nephron. On the other hand, removal of creatinine depends on filtration alone, which is thus an accurate indicator of glomerular filtration function.

Clinical Course of Acute Renal Failure

Initial Period

At the outset the surgeon should be aware of the causes primarily responsible for ARF especially when one's aim is prevention of established intrinsic parenchymal renal failure (ATN). After the initial stage of shock, ARF is manifested by one of the following:

- **Reversible** functional prerenal oliguria (dehydration) or established organic renal oliguria associated with ATN.

- **False** anuria associated with urinary retention or an obstructed Foley's catheter. "True" anuria is seen with prerenal vascular obstruction, ATN, bilateral cortical necrosis and obstructive uropathy.

- Non-oliguric ARF (high-output renal failure) which coincides with the diuretic phase of ARF (> 2000 mL/24 hours), accounts for 25% to 80% of all medical cases of ARF. The reason for the high frequency of occurrence of non-oliguric ARF may be explained by:

- Daily biochemical monitoring of seriously ill surgical patients, regardless of the amount of urine output.

- Aminoglycoside nephrotoxicity which is mainly a hospital-acquired ARF.

- Prophylactic usage of potent diuretics and vasodilators in shocked patients.

- Early aggressive resuscitation and supportive measures in the seriously ill, septic and

shocked patients.

- Early aggressive fluid resuscitation of the severely traumatized and burnt patient.

Oliguric Period

The period of oliguria usually lasts for 7-21 days (sometimes 6 weeks) before entering the diuretic phase. As the kidney is responsible for the maintenance of the àmilieu interieurà (water and electrolytes, acid-base d excretion of the metabolic and products of protein metabolism) the concentration of these substances may rise during the oliguric period of ARF leading to the uraemic syndrome. It consists of urea, creatinine, uric acid, organic acids, potassium, magnesium and many other products of protein metabolism.

For assessment of kidney function, the serum creatinine is a more accurate indicator of the blood urea nitrogen concentration, which is effected by the rate of excretion, dietary intake, rate or protein synthesis and tissue catabolism. The normal rise of blood urea nitrogen is approximately 3.5 mmol/L/24 hours. In many post-operative patients a daily rise of blood urea nitrogen may reach levels of 25 mmol/L and are classified as hypercatabolic oliguric ARF. This group normally carries a higher mortality rate in spite of active medical intervention.

Many of the substances responsible for the clinical signs and symptoms are of small molecular weight and are freely dialyzable.

The uraemic syndrome seen in ARF is manifested by deranged function of almost every organ as outline in Table 1.

Diuretic Period

At the end stage of the oliguric period, diuresis may appear abruptly or set in at a more gradual pace over several days. The prior state of hydration determines the degree of diuresis and varies between 2-10 L/day. It may lead to a dehydrated, salt depleted patient (hypokalaemia) requiring strict medical attention. During this period the patients clinical condition may become worse with confusion, vomiting, abdominal pains and hyperreflexia.

Generally the blood urea rises for approximately 3 days after the onset of diuresis and then gradually decreases to normality. There is a loss of sodium and potassium and an outpouring of casts in the urine.

Pathophysiology

Normal renal function depends on adequate renal perfusion maintaining an intact GFR and oxygen supply for the active ion transport mechanisms. Normal glomerular filtration is regarded as the initial step in the renal excretion of most of the metabolic waste products. ARF results from a derangement of the renal circulation, glomerular or tubular function, proceeding to an acute onset of azotemia.

Functional Reversible Prerenal ARF

The self-protecting process of autoregulation enables the kidney to withstand relatively large changes in perfusion pressure by keeping renal blood flow and GFR near normality. Prerenal ARF occurs when autoregulation fails to maintain a normal GFR in response to diminished renal perfusion. This commonly occurs in the clinical setting of true volume depletion (i.e. extracellular fluid or bloodloss), "pump" failure (congestive heart failure) or diminished "effective" intravascular volume due to hypo-albuminaemia (i.e. cirrhosis or burns). Prolongation of hyopoperfusion leads to an intrinsic renal failure with permanent suppression of GRF resulting in azotaemia. A decreased perfusion also involves an increased reabsorption of water and solutes throughout the nephron. The subsequent increase in peritubular oncotic pressure leads to an increased proximal tubular reabsorption of sodium and fluid with low urine-sodium concentrations. Renin secretion is increased leading to increased aldosterone levels ultimately increasing sodium reabsorption along the distal convoluted tubule. Increased renal sympathetic nerve activity may complement the above-mentioned mechanism. In response to a low circulating volume, antidiuretic hormone is released, stimulating water reabsorption by the collecting tubule.

The final outcome is oliguria, low urinary sodium concentration with increased urinary osmolarity. With defective antidiuretic hormone secretion normal urine volumes and isosthenuria exist if urine concentration ability is impaired. Urinary sodium concentration remains low. Rapid correction of renal hypoperfusion using active fluid resuscitation measures lead to resolution of azotaemia. The inability to diagnose prerenal failure may result in persistance of renal hypoperfusion and the development of intrinsic parenchymal ARF.

Intrinsic Parenchymal ARF

It is characterized by an abrupt decrease in GFR and tubular function presented by oliguria, isosthenuria, azotaemia and increased urinary sodium excretion.

The pathogenesis of intrinsic parenchymal renal failure appears to be multifactorial. Virtually any renal insult may result in ARF and the following categories may cause intrinsic parenchymal ARF.

- Acute tubular necrosis (ATN) includes those entities that cause ARF by ischaemic or toxic damage to the kidney. Following tubular cell injury the following factors contribute to decreased GFR maintaining renal dysfunction:

1. Intratubular obstruction by cellular debris resulting in an increased intratubular pressure.

2. Persistent efferent arteriolar vasoconstriction.

3. Backleakage of luminal fluid across the damaged tubular epithelium.

4. Possible alterations in glomerular membrane size and permeability.

5. Congestion within renal vasculature.

- Other forms of intrinsic parenchymal ARF include glomerular or renovascular disease, interstitial nephritis and intrarenal crystal deposition.

- Cell damage and necrosis.

Non-Oliguric ARF

According to experimental evidence non-oliguric ARF occurs both due to a failure to generate a hypertonic medullary interstitium and a decreased sensitivity of collecting tubuli to antidiuretic hormone (ADH).

Acute Diffuse Interstitial Nephritis

Differential Diagnosis

Deterioration of renal function post operatively usually comes to the surgeon's attention because of oliguria, anuria, abnormally high output and azotemia. A systematic clinical and biochemical approach to such a patient is of utmost importance. The pre- and post-renal causes should first be excluded before concluding that intrinsic parenchymal renal tubular damage has occurred because specific therapy may be curative.

Total Fluid Volume

Careful assessment of total body-fluid volumes by clinical examination is of utmost importance. Haemodynamic alteration of kidney perfusion due to hypovolaemia or vasoconstriction (hypotension) leads to prerenal failure. Helpful bedside observations assessing extracellular fluid volume depletion of these patients include intake and output records, dry mucous membranes, decreased skin turgor, tachycardia, postural changes in blood pressure and pulse, and the presence of supine jugular venous distension. On the contrary, elevated jugular venous pressure, basal rales, a third heart sound and peripheral oedema, indicate hypervolaemia and/or heart failure seen with ARF. If available, central venous pressure (cvp) or pulmonary artery wedge pressure via Swan Ganz catheterization, may be helpful adjunct to physical examination in assessing intravascular volume.

Urinary Output

The volume or urinary output per day may yield important diagnostic clues.

The average urinary flow during established ARF is < 400 mL/day, total anuria (< 100 mL/day) uncommon with ATN, suggest obstructive uropathy or glomerulonephritis. Variations in daily urine output may signify partial urinary tract obstruction. Non-oliguria (> 2000 mL/day) is particularly seen with nephrotoxic injury and accounts for 25% to 30% of cases. This is also seen after oligaemia and successful resuscitation.

Urinary Changes Associated with ARF

Urinalysis

Urinalysis may give additional information in the differential diagnosis of ARF.

- **Prerenal failure:** A urinary sediment is present where hyaline and finely granular casts dominate or are often normally found.

- **Intrinsic parenchymal renal failure (ATN):** Established ARF is usually associated with coarse granular and tubular epithelial casts. Pigmented casts are seen with haemoglobinuria and myoglobinuria ("crush" syndrome). Crystals may be associated with acute urate or oxalate nephropathy.

- **Obstructive uropathy:** It is usually accompanied by a clean urinary sediment, except when urinary infection or renal stones are present.

Urine Chemistry

Chemical Composition

The chemical composition of the urine is the cornerstone in the diagnosis of the oliguric azotaemic patient.

- **Urinary sodium and chloride levels:** Caution should be used in patients receiving loop (furosemide) or osmotic diuretics (mannitol) leading to false high concentrations of sodium and chloride, making interpretation of results difficult.

1. *Prerenal failure:* The proximal and distal renal tubules conserve solutes and water as renal perfusion decreases, leading to low urinary sodium and chloride levels (< 10 mEq/L).

2. *Intrinsic parenchymal renal failure (ATN):* Because of renal tubular dysfunction, patients are unable to conserve urinary sodium. This leads to high urinary sodium levels, exceeding 40 mEq/L.

3. *Non-oliguric renal failure:* Urinary sodium and chloride are not sensitive indicators as the concentration can be extremely variable in this group of patients.

4. *Postrenal failure:* Urinary chemistry values in postrenal failure are remarkably similar to those found in acute tubular necrosis. This emphasizes the absolute need to exclude obstructive uropathy in ARF. Ultrasound, DTPA, renogram, or computed tomography may be used to exclude postrenal obstruction.

- **Fractional excretion of sodium (FEna):** A normal kidney excretes only 1% of filtered soium in urine (99% reabsorbed by the proximal and distal tubuli). FEna measures the percentage filtered sodium excreted into the urine - measuring tubular function. Fractional excretion of sodium (FEna) = Una x Pcr/Ucr x Pna.

1. *Prerenal failure:* FEna is usually less than 1% in prerenal failure, indicating that 1% of filtered sodium is excreted into the urine.

2. *Intrinsic parenchymal renal failure (ATN):* FEna is usually greater than 3% in acute tubular necrosis and non-oliguric ARF. This signifies an inability of the tubuli to conserve sodium.

3. *Postrenal failure:* FEna is usually greater than 1% in cases with obstructive uropathy.

- **Renal failure index (RFI):** The RFI is the product of urinary sodium and plasma creatinine levels divided by the urinary creatinine level: RFI = (Una x Pcr)/Ucr.

1. *Prerenal failure:* RFI is usually less than 1 in prerenal failure.

2. *Intrinsic parenchymal failure (ATN):* RFI is usually greater than 1 in ATN.

3. *Postrenal failure:* RFI is usually greater than 1 in cases with obstructive uropathy.

- **BUN/creatinine ratio:** The fact that urea (filtered by glomeruli and reabsorbed by tubules) and creatinine (filtered by glomeruli and secreted by distal tubules) are handled differently by the kidney, enables the surgeon to use the BUN/CR ratio diagnostically.

1. *Prerenal failure:* Caused by maximal reabsorption of urea, due to decreased renal perfusion. A BUN/CR ratio of 20:1 is reached in the prerenal oliguric patient.

2. *Intrinsic parenchymal renal failure (ATN):* A normal ratio of 10:1 is commonly seen in patients with ATN, due to the non-functioning renal tubules.

- **Urinary/plasma (U/P) ratio of urea and creatinine:**

1. *Prerenal failure:* High concentration of solutes in low urine volumes is commonly seen in patients with prerenal failure. U/P ratios of urea and creatinine will reach levels of approximately 20 and 40, respectively.

2. *Intrinsic parenchymal renal failure (ATN):* U/P ratios of urea and creatinine will reach levels of 5 and 10, respectively.

3. *Non-oliguric renal failure:* U/P ratios of urea and creatinine may be sifgnificantly higher in non-oliguric patients although still lower than in patients with prerenal failure.

Urine Osmolarity

- **Prerenal failure:** In the prerenal azotaemic patient, relative hyperosmolarity exists (intact functioning renal tubules) with a specific gravity of urine above 1,015, urine osmolarity above 400 mOsm/L and urine to plasma osmolarity ratio (U/P osm) in excess of 1.5.

- **Intrinsic parenchymal renal failure:** The renal tubules are unable to concentrate or dilute urine in patients with ATN. The urine is therefore isosthenuric with a urine osmolarity of 300 mOsm/L. The U/P osm ratio approximates 1.

Figure 3.13.1 gives a broad outline of the clinical approach to the acutely oliguric and azotaemic patient.

Table 3.13.1. Systemic manifestations in acute renal failure from Schwartz

Organs	Systemic manifestations
Neurologic	*Central:* Agitation, loss of memory, apathy, delirium, coma, convulsions, *grand mal* or Jacksonian type
Haematological	Bleeding diathesis, leukocytosis in absence of infection
Cardiovascular	Uraemic pericarditis, toxic myocardiopathy, hypertension (renin induced and overhydration)
Respiratory	Uraemic pneumonitis, uraemic pleuritis, respiratory insufficiency
Gastrointestinal	Anorexia, weight loss, nausea, vomiting, uraemic gastritis, uraemic colitis, parotitis, stomatitis
Cutaneous	Pruritus, uraemic frost
Musculoskeletal	Secondary hyperparathyroidism with osteoporosis to osteitis fibrosa cystica, pseudogout, metastatic calfication in tendons
Ocular	Conjunctivitis (red eye of uraemia). Retinal oedema (due to overhydration), retinal detachment (due to hypertension)
Systemic	Acidosis, glucose intolerance and secondary infections.

Radiographic Studies

If the diagnosis has not been ascertained after thorough clinical examination, blood and urine tests then sophisticated radiographic studies are mandatory.

Scout Film of Abdomen

It is a simple and safe method of demonstrating kidney size, radio opaque renal and ureteric stones and the presence of longitudinal calcifications of an abdominal aortic aneurysm creating renal artery obstruction.

Ultrasonography

Ultrasonography is a safe non-invasive effective way of demonstrating hydronephrosis with or without renal calculi in postrenal ARF. It should be the initial screening method and usually backed up with an excretory urogram, isotope renography, computed tomography or antegrade or retrograde pyelography.

Radionuclide Scan

DTPA (diethylenetriamine pentacetic acid) renograms are used to study renal perfusion, function and obstruction in patients with ARF.

If renal perfusion cannot be determined, renal arteriography is indicated to demonstrate renal artery obstruction.

Renal Biopsy

Renal biopsy in ARF is reserved for those patients where the diagnosis of ATN appears uncertain or recovery is delayed for 3 to 4 wseeks. This is to exclude intrinsic renal disease (glomerulonephritis) or bilateral cortical necrosis. Percutaneous needle biopsy of the kidney is contraindicated in the presence of bleeding diathesis or uncontrolled hypertension.

Table 3.13.2 summarizes the differentiation between oliguric ARF, non-oliguric ARf and prerenal azotaemia.

Table 3.13.2. Differentiation between oliguric ARF (ATN), non-oliguric ARF and prerenal azotaemia

Azotaemia	Oliguric	Non-oliguric ARF (ATN)	Pre-renal ARF
Clinical	Well-hydrated or overload	Dehydration, hypotension	Dehydration, hypotension
Urine volume	50-400	400-3000	50-800
Urinary sediment	Pigmented cellular casts, epithelial cells	Equivocal	Usually normal
Urinary sodium	>40	Variable	>10
Fractional excretion of sodium (FEna)	>7	>3	<0.5-1
Renal failure index (RFI)	>1	>1	<1

Serum BUN/Cr	10	10	20
U/P urea	<5	<10	>20
U/P creatinine	<10	<20	>40
Specific gravity	1,010-1,015	1,010-1,015	>1,015
Urine osmolality	300	300	>400
U/P osmolarity	<1,1	<1,1	>1,5

Management of ARF

Initial Period

Prevention

Having failed to reduce the mortality of overt ARF, prevention has become the watchword. ALthough the pathogenesis of ARF is still continuous and ill-understood, the following factors need consideration as effective preventative measures.

General Preventive Measures

Pre-existing conditions associated with reduced renal perfusion present an increased risk of ARF when exposed to potentially nephrotoxic drugs or transient renal ischaemia and should be prevented.

Recognition of High-Risk Patients

- Advancing age: Patients exceeding 65 years.

- Extracellular fluid volume depletion with or without shock.

- Sepsis, with special reference to intra-abdominal sepsis and hypercatabolism.

- Type of surgical procedure (Table 3.13.3).

- Circulatory failure (i.e. hypovolaemic septic or cardiac shock).

- Gastrointestinal bleeding.

- Single or multiple organ system failure - heart, liver, lung or kidney failure and CNS malfunction (table 3.13.4).

- Severe generalized atherosclerotic disease.

- Myocardial infarction of recent origin.

Recognition of Patients Taking Potential Nephrotoxic Agents

The role of non-steroidal anti-inflammatory agents (NSAIDs), aminoglycosides and a contrast load in dehydrated and diabetic patients increases the risk of patients developing ARF. It should alert the surgeon to assess the risk/benefit ration before administering these agents.

Recognition of General Risk Factors

- Pre-existing renal insufficiency
- Diabetes mellitus
- Myeloma
- Dehydration
- Prior acute renal failure
- Hyperuricaemia
- Congestive heart failure
- Trauma
- Contrast load
- Hypertension
- Obesity
- Alcoholism

Specific Preventive Measures

Prevention of Postoperative ARF

Considering the pathophysiology of ARF several steps should be taken to prevent this complication (table 3.13.5).

Table 3.13.5. Prevention of Postoperative ARF

Principle	Method
Monitor renal function	Serum creatinine Serum BUN Urinary output

Assess volume status	Physical examination Serial body weights Central venous pressure Pulmonary capillary wedge pressure
Control bloodpressure	Intra-arterial monitoring Avoid hypotension (dopamine, isoproterenol) Reverse severe hypertension (nitroprusside)
Optimize cardiac function	Monitor cardiac output Afterload reduction Inotropic agents
Relieve urinary obstruction	Prompt radiographic diagnosis Catheter drainage Surgical correction
Avoid nephrotoxins	Limit radiologic contrast Aminoglycoside drugs, NSAID
Prevent sepsis (i.e. hypercatabolism)	Catheter care Abscess drainage Isolation techniques Antibiotics
Consider diuresis	Mannitol Frusemide Dopamine
Treat hypovolaemia	Saline, blood or plasma.

Specific Preventative Measures Adopted to Reverse Incipient ARF (IARF)

Table 13.3.6 summarizes the diagnosis and management of ARF.

Table 13.3.6. Management of Acute Renal Failure

Cause	Diagnosis	Management
Prerenal azotaemia Urine/plasma	Normal-sized kidneys Urinary Na+ < 20 mmol/L osmolarity > 1.5 RFI < 1 FENA < 0.5-1	Replace fluid loss Frusemide or dopamine if no diuresis Treat cardiogenic shock
Postrenal obstruction with	Anuria Palpable bladder Large kidneys	Bilateral nephrostomies to relieve obstruction Foleys catheter

azotaemia	Dense nephrogram Sonography to determine obstruction Antegrade or retrograde pyelogram,CT scan to determine site of obstruction	Surgery to relieve obstruction Steroid for retroperitoneal fibrosis
Renal azotaemia (ANT)	Normal-sized kidneys Urinary Na+ > 40 mmol/L Urine/plasma osmolarity < 1.1 RFI > 1	Correct reversible factors (nephrotoxic drugs, hypertension, sepsis DIC, myoglobinuria) Fluid and electrolyte balance, frusemide, and dopamine Dialysis
Bilateral renal artery or vein occlusion	Absent renogram Angiography	

Prerenal Failure

Replacement of intravascular fluid deficits is critical in patients with prerenal failure. Early recognition and treatment can prevent the progression to intrinsic established renal failure.

The oliguric patient with hypovolaemic prerenal failure is corrected with fluid that has been lost (i.e. colloid or crystalloid). The efficacy of volume replacement is monitored by clinical signs, CVP and wedge pressure and its success is reflected by an increase in urine production (urine output > 30 mL/hour).

If all repletion measures have been comleted, and there is still no increase in urine voume, it is reasonable to use diuretic agents to promote urine flow and reverse early ARF. The most favoured diuretics are the loop diuretics (furosemide and ethacrynic acid) and osmotic diuretics (mannitol).

The dose of furosemide should not exceed 200 mg (as this can lead to deafness) and a single dose of 12.5 g of mannitol intravenously may lead to fluid overload. Dopamine, a renal vasodilator, should be part of either regimen at low rates of infusion (1-5 U g/kg/min). These measures may reverse oliguria in patients with hypoperfusion or lead to non-oliguric renal failure which has been shown to have a more favourable prognosis.

Postrenal Failure

Depending on the site of obstruction, relief of obstruction may simply require bladder catheterization or percutaneous nephrostomies as an emergency procedure. Definitive surgical procedures are delayed until renal function has improved. Dialysis is indicated prior to the above procedures in extremely ill hyperkalaemic patients or where established ARF has

evolved.

Period of Oliguria and Anuria

Management of Established ARF

The principles of management of established ARF are the same, regardless of the underlying cause. At present, the leading causes of death are infection, haemorrhage and complications of the underlying disease which need special attention and treatment.

Initial Management

Early and complete debridement (i.e. amputation of limbs if indicated) with correction of the fluid and electrolyte status of the patient. Relook laparotomies are absolutely essential.

Hyperkalaemia

Of all the electrolyte abnormalities, hyperkalaemia is the most serious and requires urgent appropriate treatment.

Rapid increase of serum potassium may be seen, especially in hypercatabolic patients (septic, necrotic or devitalized tissue). Hyperkalaemia is asymptomatic but leads to ECG changes which include peaked T-waves, prolongation of PR intervals, loss of P waves and widening of the QRS complex, indicating imminent cardiac arrest. When significant ECG changes are apparent, emergency treatment is indicated (table 7).

Table 3.13.7. Management of Hyperkalaemia

Substance	Dose	Onset of effects	Duration of effects
Prophylactic			
Kayexalate	30-60 oral	1-2 h	4-6 h
Emergency treatment			
Ca gluconate	2-10 g IV	Min	30-60 min
Sodium bicarbonate	45-90 mEq IV	Min	1-2 h
Hypertonic glucose and insulin	25-50 gm IV 10-29 units	Min	2-4 h
Kayexalate	50-60 g Retention enema	30 min	4-6 h

Daily serum potassium levels should be measured (especially in hypercatabolic states). If less than 6 mmol/L, Kayexalate, a cation exchange resin, (10 g twice daily) is given orally or per enema. Serum potassium levels above 6 mmol/L are an absolute indication for temporary emergency treatment.

Fluid Volume and Electrolyte Requirements

Volume overload, another concern in the patient with ARF, can be prevented by limiting total fluid intake to 500 mL/day plus visible urine, gastrointestinal and third-space output. Careful monitoring of the clinical state of hydration, fluid intake and output with accurate weighing twice daily, prevents this complication. A weight loss of approximately 0.5 kg/day due to catabolism of body tissue, indicates adequate fluid restriction. The daily requirements of sodium and potassium should not exceed 60 mmol/day.

Hyponatraemia

Hyponatraemia occurs when administration of hypotonic intravenous fluid exceeds free water elimination. The hyponatraemia is a contributing factor to the encephalopathy and convulsions that complicate ARF at a sodium concentration below 120 mEq/L. Management of florid hyponatraemia consists of free water restriction and dialysis. Hyponatraemia is best managed by effective prevention.

Metabolic Acidosis

Isolated acidosis is seldom a problem but may complicate ARF associated with hypercatabolism with sepsis, trauma or major surgery. Potential harmful effects of progressive metabolic acidosis are nausea, vomiting, cerebral dysfunction, cardiac depression, insulin resistance, and hyperkalaemia. Treatment consists of dialysis, debridement of infected tissue (lowering the hypercatabolic state) and not hypertonic sodium bicarbonate, which may precipitate pulmonary oedema in the oliguric and/or anuric patient.

Hypocalcaemia and Hyperphosphataemia

Tissue necrosis from crush injury or burns may be complicated by hypocalcaemia (ionized calcium usually near normal owing to azotaemia, acidosis and hypoalbuminaemia) and hyperphosphataemia. Management consists of magnesium-free phosphate-binding antacids and dialysis (dialysate calcium concentration of 3.25-3.50 mEq/L).

Dialysis

It should be remembered that dialysis is best initiated prophylactically and not as an urgen procedure which is usually associated with life-threatening complications.

The specific indications for dialysis are clinical and biochemical and are outlined in table 3.13.8.

Table 3.13.8. Specific indications for dialysis in ARF

Clinical Indications
- Uraemia: Early signs of deterioration - anorexia, nausea, change in mental status, neuromuscular hyperirritability, increased bleeding tendencies.

- Overhydration: Pulonary oedema, "uraemic" pneumonitis, refractory oedema.

Biochemical Indications

- Blood urea level reaches 25-30 mmol/L

- Serum creatinine > 500 mmol/L

- Serum carbon dioxide < 15 mEq/L

- Hyperkalaemia

It is now well-established that the maintenance of the blood urea at levels below 33 mmol/L in ARF reduce the incidence of complications dramatically. Therefore therapy should be instituted before this level is reached.

Peritoneal Dialysis

This is a safe and simple procedure, but carries some risk of peritoneal infection. It is less efficient for the extraction of urea, and creatinine, but more efficient for the removal of excessive fluid (hypervolaemia). It is indicated in the hypervolaemic patient with mild uraemia and contra-indicated in those with recent abdominal surgery with hypercatabolism.

Haemodialysis

This is more effective than peritoneal dialysis. It is indicated in all surgical patients. It may be hazardous in patients with bleeding tendencies or unstable bloodpressure.

Management of Non-Oliguric Renal Failure

Considerable interest has centred on non-oliguric ARF due to its fewer complications and low mortality as compared to its oliguric counterpart. Early diagnosis is important both for the management of fluid, drugs and electrolytes, as well as for correcting the offending agent.

Management of Late Complications of ARF

Inadequate Nutrition

Oral feeding is best if it can possibly be undertaken, but intravenous feeding is now almost always indicated as so many patients are on ventilators or have gastrointestinal problems. This leads to less protein catabolism and depression of the immune response. The amount of calories required will depend on the rate of catabolism. Basal metabolic energy requirements for adults are 25 kcal/kg/day. During hypercatabolic states (major surgery or trauma) 40-50 kcal/kg/day are needed. Burnt patients require 60-75 kcal/kg/day.

Infection

This is the most common late complication and occurs in 90% of ARF cases. It is a result of the severely compromised resistance of these patients. Infection surveillance should be a daily routine (infected vascular lines, Foley catheters, etc) and identified infections are treated promptly before culture results are available.

Gastrointestinal Bleeding

This may account for up to 20% of deaths. Better dialysis and nutrition have probably contributed as much as prophylactic antacids and H_2 receptor antagonist to the virtual disappearance of this complication.

Drug Administration

Patients with ARF normally require drugs excreted by the kidneys. Therefore before prescribing a drug one should be familiar with its pharmacokinetics and avoid nephrotoxic drugs.

Anaemia

A frequent complication which may need transfusions for active blood loss or during the convalescence period.

Pulmonary Oedema

This is usually precipitated by excessive parenteral fluid administration, mannitol or altered vascular perfusion. If conservative measures are unsuccessful, early effective dialysis is instituted.

Period of Diuresis

During the period of diuresis, mortality can occur due to impairment of electrolyte balance but this should be prevented. Strict clinical and biochemical supervision is therefore mandatory.

Renal Function After ARF

Return to normality is seen 3-6 months after the acute insult. The degree of return of renal function depends on the degree of permanent cell damage with interstitial fibrosis.

The last renal function to return to normal is the concentrating ability of the renal tubules. In a small group of patients loss of the nephron populations may result in a decrease in glomerular filtration rate (80% at 6 months) and renal blood flow, with intact tubular function.

Prognosis

The final outcome depends on the cause and type of ARF. In spite of advances in ventilation, antibiotic chemotherapy, early diagnosis, cardiovascular monitoring, dialysis and

nutrition, mortality among surgical patients with oliguric ARF (50-60%) remains higher than among medical patients (3%) and patients with nonoliguric ARF.

Mortality has been lowered primarily by active preventative measures rather than by improvements in the treatment of established ARF, where many complications develop.

Comment

Acute Renal Failure

A. M. Meyers

The aforegoing chapter on acute renal failure (ARF) has been written by a surgeon for surgeons and, as such, contains all that is necessary for students, registrars and consultants in all branches of the surgical discipline. It represents a comprehensive, well written, practical and yet scientific approach to an important and yet still poorly understood problem frequently encountered in all fields of surgical endeavour. The following additional points are intended to reinforce and expand some of what has already been said as well as to introduce a few new concepts which have or will soon have important practical connotations. Additional references have been appended for the interested reader. The following aspects will be discussed as applied to ARF in the surgical discipline.

- Mechanisms of prerenal failure and renal failure

- Drug-induced nephropathy

- The limitation of diagnostic indices

- Special surgical settings

- Newer aspects of therapy

- Prognostic and risk factors

Mechanisms of Prerenal and Renal Failure

Prerenal uraemia is a grossly simplified concept of complicated adaptive processes by the kidney which often, but not always, takes place prior to the base of established ARF. In addition, it has now been established that there is another step to be considered, i.e. that of **pre-prerenal failure (PPRF).**

Indeed, PPRF, although also not always present, may well be the most important phase for the clinician to be aware of and to diagnose. Briefly, the concept is as follows: Due to intrarenal regulatory phenomena, the GFR is maintained at normal or near normal despite a significant drop in circulating blood volume of cardiac output. The most important mechanisms here are:

- The autoregulatory response of the afferent arterioles to reductions in perfusion

pressure by a myogenic response culminating in proximal arteriolar dilation. Therefore, without change in the tone of the efferent arteriole, glomerular perfusion pressure will be maintained. This response is reinforced by the salutary effecxts of the tubuloglomerular feedback system.

- At this time, two further physiological adaptive processes occur. Locally produced angiotensin II (Aii) which is produced in response to hypovolaemia, although tending to produce afferent arteriolar spasm (i.e. thus attempting to overcome the myogenic response) actually causes relatively more vasoconstriction in the efferent than in the afferent arteriole. This phenomenon counterbalances the overall constrictor effects of angiotensin II and results in the maintenance of a normal transglomerular filtration pressure albeit at the expense of a decline in total glomerular plasma flow.

- The intraglomerular production of angiotensin II and of other vasoconstrictor agents would, if allowed to go unopposed, eventually result in a decrease in the GFR. Counterbalancing these mechanisms is the renal prostaglanding system which, under normal conditions probably plays no or little physiological role. However, local prostacyclin and PGE_2 production is switched on in situations of a decrease in the extracellular fluid volume or a decrease in renal perfusion pressure. These PGs then exert a modulatory effect on the afferent, efferent and glomerular capillaries by limiting the degree of local vasoconstriction. The stimuli to produce PGs are mediated via A II.

- Local endothelial-derived vasoactive substances: Recently two new sets of opposing peptide substances with both endocrine and autocrine properties were discovered. These are endothelium-derived relaxing factor (EDRF) and endothelin both of which are manufactured by endothelial cells. It is interesting to note that in certain pathological situations, release of EDRF is inhibited by hypoxia or reperfusion. It is these stimuli which result in the release of endothelin, a substance which has been shown to be far more potent and long-lasting with respect to constrictor effects when compared with angiotensin II. It is conceivable that both substances play a role in the genesis of ARF, i.e. the role of EDRF in the early myogenic afferent arteriolar relaxation versus later endothelin-induced vasoconstriction. More work is required to elucidate the precise mechanisms.

From the practical aspect, however, the diagnosis of PPRF should be entertained under the following circumstances:

- A clinical suspicion in patients at risk.

- A normal, at worst, a mild reduction of the creatinine clearance (serum creatinine will still be normal).

- A low (< 20 mmol/L) urine sodium.

It is easy to postulate that, for a period of time, the phase of PPRF is delicately poised and that several stimuli could adversely shift this effective form of intrarenal compensation into the phase of prerenal failure (PRF) which is characterized by reversible azotemia. Factors which may precipitate this change are:

Continuing Hypovolaemia, i.e. Inadequate Resuscitation

A systolic BP of ± 80 mm Hg is the critical pressure below which effective renal blood flow will be severely compromised. However, this pressure may well be much higher depending on the previous state of the renal vasculation, i.e. in the hypertensive or elderly, this pressure could be considerably higher so that a BP is 120/70 may represent shock in these individuals. It is possible that some individuals with previous vascular pathology (i.e. hypertensives, those in cardiac failure, diabetes) may never go through the phase of PPRF but progress directly to PRF or even to tubular necrosis.

Injudicious Therapeutic Intervention

Injudicious therapeutic intervention in PPRF, i.e. without adequate resuscitation, may hasten the advent of PRF or ARF:

- Intravenous contrast media given at this critical time.

- Drugs which themselves reduce GFR, i.e. non-steroidal anti-inflammatories (NSAI), cotrimoxazole, cyclosporine, demeclocycline.

- Drugs inducing excessive systemic vasodilatation, i.e. inappropriate use of after-load reducing agents.

- Drugs inducing vasoconstriction during this phase, i.e. norepinephrine or doses of ≥ 5 microg/kg/minute of dopamine.

- Further surgery at this time.

As a practical guideline frequent estimation of the urine sodium concentration which, if ≤ 20 mmol/L, should dictate that adequate resuscitation should be completed before any further procedures are contemplated except in life-saving circumstances.

There are two other important mechanistic aspects of ARF which are of relevance to the surgical patient but which are beyond the scope of this article and so will only briefly be mentioned. Firstly is the pathophysiology of attenuated acute renal failure. Although well-described in the postcardiac surgical patient, the entity applies to many differing varieties of surgical ARF. The reader is referred to the excellent article by B. Myers at al. Briefly, the most important aspects are: High output states, usually diagnosed as prerenal RF, which on using adequate diagnostic criteria show that these patients already have established ATN. There are 3 major patterns seen in this type of ARF each of which is influenced by the cardiac output. Patterns A and B have good outcomes but pattern C has a poor prognosis. This pattern is characterized by more severe azotemia, protracted poor cardiac function and, most importantly, a second insult, i.e. sepsis, a further operation, a bleed, a dose of a NSAI agent, etc. Many of these "secondary" insults are potentially avoidable.

Finally, the pathophysiology of obstructive uropathy has been recently reviewed and the reader is referred to the excellent article by P. R. Wilson.

Drug-Induced Nephropathy

Drugs can cause several syndromes all leading to ARF in the surgical patient.

Nephrotoxins

Aminoglycosides

It must be realized that aminoglycosides take 5-7 days before a rise in serum creatinine heralds the onset of ARF. Enzyme-uria can precede this rise by up to 72 hours. Why is age such an important factor for ARF in patients receiving aminoglycosides? The major reason comes with the appreciation of the fact that a "little old lady" with a serum creatinine of 90 micromols/L may, in fact, have a creatinine clearance of 40 mL/min! Therefore, the serum creatinine should not be used as a guide to dosage and a creatinine clearance is mandatory. Aminoglycosides are totally contraindicated in patients with cirrhosis or obstructive jaundice undergoing surgery. Other, equally or more potent, less toxic (but more expensive) antibiotics should be used.

Another important aspect is the realization that aminoglycosides are "fixed" in the renal cortex for weeks after the conclusion of treatment. Thus, the consecutive usage of 2 different aminoglycosides must be avoided. Other, often subclinical, insults (i.e. a small bleed or another operation), while not in themselves sufficient to cause ARF may, in the presence of aminoglycosides or previously administered aminoglycosides, be enough to cause frank ATN. It is probable therefore, that aminoglycosides should be completely avoided in high-risk cases as there are many other equally effective, safe alternatives available at present.

Nonsteroidal Anti-Inflammatories

Over-emphasis is impossible when stressing the fact that NSAIs are completely contraindicated in the high-risk surgical patient. Even a single dose can result in serious ARF requiring dialysis. This problem is seen most frequently in the "at risk" orthopaedic patient. In addition, it has been established both experimentally and clinically that NSAIs and aminoglycosides act synergistically to produce ARF. Therefore, this combination should be avoided if at all possible. In addition, in any state of decreased renal perfusion, a single dose of NSAI may produce severe ARF.

Radiologic Contrast Media (RCM)

Although serious and permanent RF can be induced with RCM in high-risk patients, i.e. those with myeloma or in diabetics with pre-existing renal dysfunction, the disturbances in function are usually mild and only transient. It should be realized that the newer nonionic agents are just as nephrotoxic as the ionic agents and are far more expensive! There is no doubt that 2 procedures involving contrast media which are performed with a short time of each other frequently produce serious nephrotoxicity.

Acute Diffuse Interstitial Nephritis (ADIN)

To much ADIN is a nebulous or even unheard of condition. However, ADIN has been

estimated to cause up to 10% of all cases of ARF in the surgical setting. The pathogenesis of this condition has not been fully elucidated but is thought to be due to an allergic reaction to certain drugs. The causes, clinical and laboratory features of ADIN are shown in table 3.13.9.

Table 3.13.9 ADIN

Causes	Clinical features	Laboratory findings
Penicillins	Fever	Eosinophilia
Cyclosporins	Rash	Eosinophiluria
Rifampicin	Arthralgia	Proteinuria
Sulphonamides	Abdominal pain	Renal dysfunction
Aminoglycosides	Oliguria	
Diuretics		
Allopurinol		
NSAID		

The clinical and laboratory findings are neither specific nor sensitive indices of the condition. A high index of suspicion must be entertained if ARF occurs in surgical patients treated with these agents and where other obvious causes exist. Renal biopsy is the only definitive way of proving the diagnosis and shows sheets of eosinophils in the interstitial tissue, often with varying degrees of ATN. It is important to establish the diagnosis as continued treatment with the offending drug may result in permanent renal dysfunction or even chronic renal failure. Another recently introduced technique which may help to establish the diagnosis is the presence of a highly positive renal gallium scan.

Drugs Causing Intrarenal Obstruction

Although not commonly encountered in the surgical patient, it is important to be aware of drugs or poisons which can cause ARF with tubular obstruction due to crystal deposition. The agents and the crystals are as follows:

- Ethylene glycol ingestion with oxalic acid deposition.

- Secondary hyperuricaemia seen in some haematological malignancies (i.e. multiple myeloma) or in the treatment thereof (i.e. acute lymphatic leukaemia) with uric-acid crystals.

- Methotrexate and sulphonamide crystals found especially in acid urine.

- Crystals of coprofloxacin found in highly alkaline urine (a rare complication).

Urinary Indices in the Diagnosis of ARF

Although urinary diagnostic indices have been highly recommended in some studies, other workers have pointed out the many deficiencies in the specificity and sensitivity of any of these tests, including the most highly predictive one, that of the fractional excretion of sodium. Theoretically, a fractional excretion of < 1 indicates normality or PRF, whilst that

of > 1 suggests tubular necrosis. Table 3.13.10 lists various circumstances in which false information may be obtained.

Table 3.13.10 Clinical states in which the fractional excretion of sodium may be greater or less than 1% in patients with acute renal failure

>1%	<1%
ATN (correct prediction)	RFF and PRF (correct prediction)
Pre-RRF (10% of cases)	Hepatic failure
Diuretic therapy	Cardiac failure
Dopamine infusion	Myoglobinuric ARF
Pre-existing chronic RF	Haemoglobinuric ARF
Glycosuria	After radio contrast mediums
Obstructive uropathy	Polyuric RF (10% of cases)
	ADIN (early phases)
	Obstructive uropathy

Provided that these pitfalls are borne in mind, the fractional excretion of sodium is a good predictive index of both oliguric or non oliguric ARF. Note also that these indices may be performed using a single spot-specimen of urine.

Acute Renal Failure in Special Circumstances

This category is presented in order to raise small but important practical points in each category presented.

Septic Abortion

This is a commonly encountered entity in the South African context and affects young women of all race groups. Acute renal failure is a serious and life threatening complication of septic abortion. If significant clinical improvement with conservative therapy has not been achieved within the first 24 hours, hysterectomy should be performed as an emergency procedure. The decision to operate early is strengthened by the presence of a disseminated intravascular coagulopathy and is further supported by reports of mortality rates between 30%-60% falling to about < 15% with early surgery.

Severe Head Trauma and Acute Renal Failure

Head trauma accompanied by ARF has a dismal prognosis. Decision to dialyse should be made early and, because of osmotic shifts and the possibility of hepatin-induced cerebral haemorrhage, haemodialysis should be avoided. Slow, continuous peritoneal dialysis is the method of choice.

Renal Function and Severe Burns

Glomerular filtration rates may rise to very high values in burn patients and one study reported a mean creatinine clearance of 172 ± 48 mL/min (normal = 104-120 mL/min). This

is presumably because of a high, endogenously created protein and or urea load induced by absorbed products from the burned areas. A protein load is known to alter intrarenal haemodynamics resulting in a net increase in the glomerular capillary hydraulic pressure. This will result in a shorter than normal half-life of drugs excreted primarily by glomerular filtration. Acute renal failure of the delayed type is common in burn patients and is usually a complication of severe sepsis. Aminoglycosides form the mainstay of antibiotic treatment in these patient thus containing the severity of the sepsis and hopefully therefore preventing the advent of late ARF. As these agents are excreted mainly via filtration, gross under-dosing may occur as a result of the shortened half life which, obviously, will have an adverse effect on the prevention of sepsis. Therefore, up to 40% larger doses may be necessary and, to safeguard against both possible underdosing and overdosing of aminoglycosides in this setting, *daily* monitoring of blood levels is mandatory.

Renal Failure After Open-Heart Surgery

Renal failure in this setting carries a grave prognosis. In one study, patients with post-operative serum creatinine levels of ≥ 500 micromol/L had a mortality rate of 66%. Factors predicting a poor outcome were: prolonged cardiopulmonary bypass time, hypotension, oliguria, low cardiac output states and serious intra-operative haemoglobinaemia.

Renal failure may also occur in the later post operative period in those patients with serum creatinine readings between 200-500 microg/L. These patients are nonoliguric but nevertheless have clearly been shown to have true tubular necrosis in an "attenuated" form. Should a second insult then occur due to i.e. sepsis, nephrotoxic drug reactions (i.e. inappropriate doses of aminoglycosides or administration of NSAI), heart failure, hypovolaemic shock or the necessity for further surgery, oliguric renal failure may ensue with a very high mortality rate. Again, the object of the exercise must be to recognise the high-risk patients and every attempt should be made to avoid further insults.

Acute Renal Failure in Aortic Aneurysms

No matter how shocked the patient is due to rupture of the aneurysm every attempt must be made to complete resuscitation prior to surgical intervention. In addition, in patients with aneurysmal rupture as well as cold aneurysmectomy patients, it has been shown that hypotensive episodes are markedly reduced when fluid volume is monitored intra-operatively using the Swan Ganz method of assessing pulmonary artery wedge pressures. By this method of assessing fluid requirements, the prevalence of ARF dropped from 33% to 10% and morbidity was halved.

Renal Failure and Liver Disease

Cirrhosis and ARF

None of 25 patients with alcoholic cirrhosis who were dialyzed survived in one reported series. This is the experience of others and of ourselves. Therefore, unless there is an obvious cause and evidence for the presence of reversible acute tubular necrosis, dialysis should not be instituted for these patients.

Extrahepatic Obstructive Jaundice

Here, even in the presence of biliary cirrhosis, dialysis carries a reasonably good prognosis and should be undertaken when indicated. It is well to remember that in ARF, bilirubin is not excreted and very high serum levels are frequently seen. It is also important to dialyse these patients early as the toxicity of liver and renal failure combined are additive or even synergistic.

Drugs, ARF and Liver Disease

Aminoglycosides and NSAI agents are totally contraindicated in patients with acute or chronic liver failure. In this setting the reputed incidence of ARF due to these drugs is > 30%.

Myoglobinuric (MGU) Acute Renal Failure

The surgeon associates this entity as a rule with severe crush injuries and trauma. There are, however, several other causes of MGU which the surgeon may encounter, namely, in alcoholic rhabdomyolysis, in drug addicts and in severe rhabdomyolysis seen in ultra-marathon runners. In the latter, ARF is a frequent complication of MGU especially where there has been an associated volume depletion usually combined with the ingestion of NSAIs during the race. Whenever severe muscle damage is suspected, serum creatinine phosphokinase levels should be measured, as current methods for the laboratory estimation of myoglobin are unsatisfactory.

Aspects of Treatment

General

Awareness of high risk patients and avoidance of additional insults is mandatory. Attention to detail and a problem-oriented approach should be used.

Primary Resuscitation

It is mandatory to insert a central-venous pressure line in shocked patients at risk for ARF. Blood or colloid (haemaccel) should be infused in order to attain a CVP of 15-18 cm of water. During this period a dopamine infusion of 2-3 microg/kg/minute should be infused (i.e. renal doses of dopamine). The aim is to establish a polyuric state or to convert an oliguric into a polyuric state even in the presence of a fractional excretion of sodium which clearly indicates the presence of established ATN. There is no doubt that high-output renal failure has a much better prognosis than oliguric RF.

Note also that there are 2 sets of dopamine receptors, i.e. a presynaptic group subserving a vasodilatory function and a postsynaptic group with an alpha adrenergic-like action causing vasoconstriction. It is likely that this second receptor complex may be stimulated by doses of dopamine as low as 6 microg/min and thus, as stated above, the maximum dose should not exceed 3 microg/kg/min. The infusion of dopamine should be maintained until effective function, as defined by a spontaneous fall in the serum creatinine,

has begun. However, if oliguria is not converted into polyuria within 24-48 hours, dopamine should be discontinued.

Furosemide

Only once volume depletion has been rectified, may furosemide, in doses of 100-250 mg IVI 8 to 6 hourly, be used to help establish and or maintain a high urine output. The use of renal dopamine with or without furosemide must be started early in the course of ARF. Large doses of furosemide alone do not improve renal haemodynamics or alter the urine volume or clinical outcome in patients with established acute oliguric, renal failure. Therefore, the use of furosemide without renal dopamine is not advocated.

Bicarbonate Therapy

In patients with an established metabolic acidosis who are in PPRF, PRF or early ARF, prompt correction of acidosis is recommended. There is evidence that, in doing so, progression to tubular necrosis may be avoided or, that with established ATN early correction of acidosis may minimize intracellular organelle damage. However, bicarbonate should be used with care in those with severe lung disease where a type II respiratory failure may be preempted by bicarbonate.

In addition, bicarbonate is required to alkalize the urine in patients with rhabdomyolysis and myoglobinuria in order to prevent tubular obstruction. This also applied to haemoglobinuric ARF, i.e. after incompatible blood transfusion.

The Use of Continuous Arteriovenous Haemofiltration (CAVH)

or Haemodialysis (CAVHD)

These two techniques have been recently introduced and are particularly indicated in the treatment of ARF in patients with cardiovascular instability. CAVDH is the preferred technique - see fig. 3.13.2 and fig. 3.13.3.

ARF, Hyperalimentation and Daily Dialysis

We and other have presented studies in patients with surgical ARF suggesting that aggressive dialysis and daily intradialytic hyperalimentation reduces mortality in these patients. The results are encouraging but insufficient data is available to allow comparison with other groups.

Prognosis of ARF

In spite of dialysis and many other modern advances, the mortality rate in patients with surgical ARF is still exceedingly high (around 65% in most series). Similar figures have been reported locally - table 3.13.11.

A well-known cliché is "patients don't die of ARF but in ARF as dialysis removes all the dangers of the uraemic syndrome". This is clearly incorrect as patients on chronic

maintenance HD are far from normal physiologically. Two questions must be asked - what the influences the prognosis and why have the figures not improved?

Factors influencing the prognosis:

- Polyuric versus oliguric renal failure. The importance of establishing polyuria was published many years ago. The mortality in oliguric RF of 70-80% drops to 30-35% in the polyuric patients.

- Risk factors as mentioned in the chapter.

- The number of primary insults.

- The number of secondary insults (most important), i.e. high-output postischaemic ARF in an otherwise stable patient, who then gets another ischaemic or nephrotoxic insult resulting in oliguric RF with a much worse prognosis.

- Number of organ failures.

Why have the figures not improved?

Again many clichés are used, i.e. we are dialysing sicker patients who previously would have died; better resuscitation results in the less ill patient recovering without dialysis, etc. When one realizes the many causes of acute renal failure, one must realize that this entity is nothing more than a syndrome and as such, it is exceedingly unwise to speak of the prognosis in such a heterogenous group of patients. Rather, a large number of variables must be recognized, including the causative categories, and a scoring system should be applied. Only after this can a rational approach to treatment be applied. To quote the work by Butkus, the following categories require attention:

- Demographic variables, i.e. age, sex, socioeconomic status, etc.

- Underlying cause of ARF.

- Pre-existing diseases.

- Clinical complications.

- Diagnosis and degree of severity of renal failure.

No doubt there are many more variables influencing prognosis and there is an urgent need for this problem to be resolved.

One final point which can strongly influence the outcome is the surgeon's knowledge of ARF and his willingness to become part of the management team. One's personal experience is that frequently ARF in surgical patients is regarded by the surgeon as a "medical complication" and the patient is either admitted or transferred to the medical services. In my opinion this practice is unacceptable. It behoves the surgeon to acquire a good

working knowledge of surgically-related acute renal failure and to work together with the nephrologist for the patient's benefit. In summary, these major points affecting prognoses will be:

- Adequate resuscitation.

- Always vigorously endeavour to create a high-output renal failure situation.

- Know all the high risk categories and recognize those patients.

- List all the initial insults.

- Avoid all secondary insults.

- Pay minute attention to detail.

- Daily close cooperation between the surgical or ICU team and the medical (nephrologist) team.

- Aggressive dialysis and appropriate hyperalimentation.

Chapter 3.14: Postoperative Jaundice

C. J. C. Nel, S. P. Grobler

Introduction

Jaundice in the postoperative period follows approximately 1% of surgical procedures performed under general anaesthesia. The incidence is significantly higher under certain conditions, such as open-heart surgert, pancreaticoduodenal and biliary procedures as well as portocaval shunts. Formulating the correct diagnosis and clinical management in the postoperative patient if often difficult and requires knowledge of the full spectrum of liver disease and awareness of the many different factors that may work in concert to contribute the development of jaundice.

Pathophysiology

Effects of Anaesthesia and Surgery on Liver Function

All types of major anaesthesia, including general, spinal and epidural anaesthesia, cause a reduction in hepatic blood flow (HBF). This effect is mediated either by splanchnic vasoconstriction or by decreased arterial pressure. A third variable on which the liver perfusion pressure depends is the central venous pressure (hepatic venous pressure). Surgical manipulation and trauma result in a further reduction in HBF, possibly because of reflex vasoconstriction. Intermittent positive pressure ventilation techniques may also result in decreased HBF.

Liver-Function Tests

Mild transient abnormalities of liver-function tests are common after general anaesthesia and surgery. Minor elevations, usually no more than 50% above normal, in serum levels of transaminases (AST, ALT), lactic dehydrogenase (LD), alkaline phosphatase and bilirubin may occur during the first postoperative week. These transient abnormalities are not associated with morphological alterations in the liver and probably reflect reductions in HBF, mild systemic hypotension, transient hypoxaemia or minor anaesthetic toxicity. Preoperative liver-function tests should be undertaken prior to major surgery under general anaesthesia to identify subclinical liver disease and to provide baseline values against which abnormal postoperative liver-function tests can be interpreted.

Classification

The appearance of jaundice (bilirubin > 35-50 micromol/L) in the postoperative patient usually indicates a more serious derangement of liver function. A pathophysiological classification of postoperative jaundice is presented in table 3.14.1.

Table 3.14.1. Classification of Postoperative Jaundice

A. Increased pigment load

- Haemolytic anaemia

- Resorption of haematomas

- Haemolysis of transfused blood

B. Hepatocellular dysfunction

- Circulatory failure

- Sepsis

- Anaesthetic-related

- Drug-related

- Benign postoperative intrahepatic cholestasis

- Viral hepatitis

- Pre-existing liver disease

C. Extrahepatic obstruction

- Bile-duct injury

- Choledocholithiasis

- Postoperative pancreatitis

D. Miscellaneous

- Postoperative cholecystitis

- Gilbert's syndrome

- Dubin-Johnson syndrome

- Total parenteral nutrition

- Jejuno-ileal bypass for morbid obesity

Hyperbilirubinaemia may be caused by three basic mechanisms:

- overproduction of bilirubin (increased pigment load)

- impaired hepatocellular function

extrahepatic obstruction

Several of these factors appear to contribute to postoperative jaundice, and in many cases it is difficult to establish a definitive diagnosis. One of the most important decisions for the clinician is to differentiate those patients who require surgical intervention for relief of mechanical obstruction from those with cholestasis due to liver injury, since reoperation in the latter group may be attended by very high morbidity and mortality. In general, most cases of postoperative jaundice are due to a combination of increased bilirubin load and hepatocellular dysfunction. Since the liver dysfunction almost always resolve spontaneously, an aggressive diagnostic and therapeutic approach is seldom indicated.

The temporal relationship between the onset of the jaundice and surgery is perhaps the most important factor in making an accurate diagnosis. For example, jaundice that develops within a few days of surgery should suggest such causes as prolonged hypotension during or after surgery, or brisk haemolysis. The jaundice caused by anaesthetic-related hepatitis (i.e. halothane) rarely develops before the seventh postoperative day. Viral hepatitis from transfused blood on the other hand would not be seen until at least several weeks or, more commonly, several months after surgery. Drug-induced hepatitis is often related to the institution of a new therapeutic agent but may be noted weeks to months after starting a drug. Only by combining the timing of the jaundice, the clinical situation, the physical examination, liver-function tests, and the listing of all known drugs and anaesthetic agents can the cause of the postoperative jaundice be readily determined.

Postoperative Jaundice from Increased Pigment Load

Approximately 250 to 300 mg (425 to 500 micromol) of bilirubin is produced each day in the normal adult from the breakdown of sensecent erythrocytes in the reticuloendothelial system. The liver is capable of conjugating and excreting at least several

times this amount of bilirubin. For this reason haemolytic anaemia is a rare cause of postoperative jaundice. patients with chronic haemolytic states, such as sickle cell anaemia or thalassemia, may develop more brisk haemolysis after the stress of surgery. Patients with undiagnosed glucose-6-phosphate dehydrogenase deficiency may be given various medications, including sulphonamides, chloramphenicol, nitrofurantoin and aspiring, which induce haemolysis. Haemolysis may also be induced by the stress of surgery and general anaesthesia. Alternatively, auto-immune mechanisms have been associated with haemolysis induced by other drugs, including penicillin, cephalosporins, methyldopa, quinidine and the sulphonylureas. Extracorporeal circulation may also cause haemolysis. If haemolysis is the cause of jaundice, 90% or more of the bilirubin will be unconjugated and associated with an elevated reticulocyte count and normal transaminase and alkaline phsophatase levels.

Increased bilirubin production from resorption of extravasated blood may also contribute to postoperative jaundice in patients with severe crush injuries or ruptured aneurysms.

Haemolysis of transfused erythrocytes is another cause of increased pigment load in the surgical patient. Approximately 10% of erythrocytes in a unit of bank blood stored for two weeks undergoes haemolysis within 24 hours of transfusion. Multiple-unit transfusions could therefore overwhelm the functional reserve of the liver for conjugation and excretion of bilirubin and result in jaundice. Acute and delayed haemolytic transfusion reactions may cause jaundice as well.

Hypoxaemia, sepsis, anaesthesia and hypotension all predispose to impaired removal of bilirubin, resulting in both unconjugated and conjugated hyperbilirubinaemia. Since conjugated bilirubin is excreted by the kidney, any renal function impairment would aggravate both the degree and duration of jaundice.

Postoperative Jaundice Caused by Hepatocellular Damage

The majority of cases of postoperative jaundice are due to direct hepatocyte injury. This may occur before, during or after surgery. The injury may be manifested by a hepatitis-like (hepatocellular damage) pattern in which elevations of the serum transaminases and evidence of impaired synthetic function predominate; or there may be a cholestatic (obstructive) picture characterized by marked elevations of bilirubin and alkaline phosphatase. In many clinical situations a mixture of these two patterns may co-exist.

Circulatory Failure

Hypotension and hypoxia are two frequently co-existent conditions associated with abnormal liver functions in the postoperative period, and probably account for postoperative jaundice in the majority of patients.

The bulk of the liver's 25% share of the cardiac output reaches it indirectly via the portal vein, only 30% coming directly via the hepatic artery, although each source is responsible for 50% of the organ's oxygen flux. The liver receives blood and a lower net oxygen saturation than other organs and a reduced HBF results in a further diminished nutrient flow to the liver. This effect is most severe in the hepatocytes surrounding the

efferent vein since the oxygen tension in this area is normally lower than in the periportal zone of hepatocytes. The liver is thus especially susceptible to hypotension, which causes functional and structural damage to liver cells. The incidence of hepatic dysfunction is particularly high after open heart surgery and traumatic shock.

Postoperative jaundice in this setting falls into two clinical patterns. The most common presentation is cholestatic jaundice, characterized by early elevation of the bilirubin on the second or third postoperative day, with peak levels of 85-500 micromol/L occurring on the seventh to tenth day. The alkaline phosphatase may be normal or only slightly elevated and the transaminases are elevated two to three times above normal. This pattern is indistinguishable from postoperative intrahepatic cholestasis (vide infra) and appears to be caused by a combination of increased pigment load from multiple transfusions and mild hepatocellular dysfunction caused by transient hypotension and hypoxaemia. Another, more severe, pattern of postoperative jaundice occurs in patients with prolonged shock lasting 12 hours or longer. In these patients, the onset of jaundice is delayed to seven or more days following surgery, and is accompanied by laboratory evidence of severe centrilobular hepatocellular necrosis with peak serum transaminase levels of 1000 units or more. Marked elevations of serum bilirubin may also occur. Although the liver is exceptionally sensitive to changes in perfusion, it is remarkably resilient and may recover completely after a transient hypoxic episode. If patients with this type of liver damage can be supported through other complications of hypotension or hypoxia such as renal failure, sepsis or myocardial failure, the jaundice will subside gradually and spontaneously. If, however, the hypotension and hypoxia are prolonged and cannot be corrected, signs of true liver failre may appear. These include a continued rise in the bilirubin level, prolongation of the prothrombin time and, finally, development of coma. Fortunately this is an exceptionally rare event. When it does occur, it is in the setting of multiorgan failure.

Congestive heart failure, from the clinically florid to the more subtle varieties, can cause hepatocellular dysfunction and jaundice in the postoperative period. Patients with elevated right atrial pressures before and after open heart surgery are particularly prone to develop perivenular necrosis.

Sepsis

Many systemic infections produce functional and structural changes in the liver. The onset of hyperbilirubinaemia commonly coincides with the appearance of septic complications after trauma or operation and is an almost universal occurrence in septic shock and multiorgan failure. Proposed mechanisms include circulatory inflammatory mediators and microaggregates, endotoxin, hepatocyte metabolic derangement and Kupffer cell dysfunction. However, there may be many other causes of liver dysfunction during sepsis including fever, hypoxia and combined hepatic and systemic involvement.

Liver-function tests typically show a rising serum bilirubin peaking at 80 to 180 micromol/L and alkaline phosphatase two to three times elevated with mild to moderate elevations of AST, ALT and LD. Liver histology shows intrahepatic cholestasis and little evidence of hepatocyte necrosis.

Management is supportive and directed at control of the sepsis and associated

conditions.

Anaesthetic-Related Liver Disease

Anaesthetic hepatotoxicity is an unusual problem occurring in approximately 1 in 10.000 patients who receive halogenated anaesthetic agents, particularly halothane and methoxyflurane and, less commonly, after enthrane, for the first time. Multiple exposures to halothane, particularly within a short time, may increase the incidence and severity of the hepatitis.

The pathogenesis of halothane-induced hepatotoxicity remains obscure. Reactive intermediate metabolic products may serve as haptens causing sensitization of susceptible individuals. Fulminant hepatic damage, which probably specifically characterizes immunological reactions, has been reported in 1 in 36.000 halothane anaesthesias. Accumulation of highly reactive (toxic) free radical metabolites of halothane may produce direct hepatic damage by a variety of mechanisms. Hypoxic stress may also be an important "trigger" in promoting hepatotoxicity.

Clinical Features

Fever typically precedes the onset of jaundice by several days, and may be erroneously attributed to infective or other causes. The onset of jaundice is quite variable, but most often occurs within three to ten days after surgery. Hepatitis which occurs more than three weeks after operation is unlikely to be related to halothane. Jaundice after a single exposure to halothane appears approximately two weeks after surgery, compared to one week after multiple exposures. The patient may complain of nausea, malaise, anorexia or right upper quadrant pain. The liver may be slightly enlarged.

Laboratory Investigations

Liver function tests reveal a conjugated hyperbilirubinaemia with peak values between 50 and 5000 micromol/L. Anicteric cases are seen and are usually associated with recovery, while bilirubin levels in excess of 170 micromol/L are associated with a poor prognosis. Serum transaminase is elevated to more than 500 units in the majority of cases, while alkaline phosphatase is seldom elevated more than twofold. The most reliable indicators of the severity of halothane hepatitis are hypoprothrombinaemia and clinical or biochemical evidence of hepatic encephalopathy. Eosinophilia and a pruritic skin rash may occur.

The major histopathological findings are acute hepatocellular necrosis, often perivenular, and a mild inflammatory exudate.

The clinical course of halothane hepatitis is similar to that of viral hepatitis except that the apparent fatality rate is much higher with a mortality of 10-40% in well documented cases of jaundice. Since there is no specific therapy for halothane hepatitis, the manegement of these patients is identical to that of massive hepatic necrosis from any cause. Corticosteroids and exchange transfusions do not seem to be beneficial in improving salvage. When recovery does occur it is usually complete, and chronic hepatitis and cirrhosis do not develop. The major goal of therapy in these patients is therefore to sustain life until the liver regenerates.

Drug-Related Jaundice in the Postoperative Period

It is often difficult to exclude drug-induced hepatitis as a cause of postoperative jaundice. Surgical patients usually receive several drugs before, during and after surgery which potentially may damage the liver.

Dose-dependent hepatotoxicity, maifested as acute centrilobular necrosis, may be found with overdoses of paracetamol, salicylates, tetracycline, azathioprine, methotrexate and cyclosporine A.

Although severe hepatotoxicity from idiosyncratic (dose-independent) drug reactions occurs only occasionally, minor hepatic dysfunction can be related to drugs in 10% or more of patients. The spectrum of illness ranges from acute or chronic hepatitis to cholestasis, although a particular drug tends to produce a specific pattern of injury.

Acute hepatocellular necrosis may be produced by isoniazid, pyrazinamide, sulphonamides, keotoconazole, methyldopa, phenytoin, and others. Drug-induced hepatitis often begins abruptly, with symptoms and signs of hypersensitivity, such as chills, fever, rash, pruritus, arthralgias and eosinophilia. Prolonged treatment with a number of drugs, particularly methyldopa, isoniazid and nitrofurantoin, can cause chronic active hepatitis.

Cholestatic hepatitis may be associated with phenothiazines, particularly chlorpromazine, erythromycin, carbimazole and the sulphonylureas. Pure cholestasis, characterized by hyperbilirubinaemia in the absence of significant parenchymal involvement or marked elevations of alkaline phosphatase, may be seen in treatment with fucidic acid, rifampicin and the synthetic estrogens and androgens. Generally the manifestations of a cholestatic type of drug hepatitis are less severe than in the hepatitic form. Cholestatic lesions, which may resolve slowly only after drug withdrawal, have to be differentiated from other causes of obstructive jaundice, both intrahepatic and extrahepatic.

Many patients are asymptomatic but have abnormal liver-function tests such as elevated bilirubin or alkaline phosphatase. Pinpointing the agent responsible, particularly if the patient is on several drugs, can be difficult; if alternative treatment is available, it should be substituted. Deliberate diagnostic rechallenge is potentially dangerous because it may precipitate a severe reaction. Liver biopsy is of limited use in diagnosis. A number of drugs, notably rifampicin and most of the anti-epileptics, are potent hepatic microsomal enzyme-inducing agents which can produce marked elevations in gamma-glutamyl transferase and some rise in alkaline phosphatase. In patients receiving these drugs such changes on their own do not necessarily signify hepatic damage.

Benign Postoperative Intrahepatic Cholestasis

The term benign postoperative cholestasis denotes a cholestatic picture that may occur in the postoperative period. The typical patient has had major surgery with multiple complications, including hypotension, haemorrhage needing several units of blood, hypoxia, sepsis, cardiac decompensation or renal failure. As already discussed, any of these factors individually is reason enough for postoperative jaundice to develop. In patients with this so-called syndrome, marked hyperbilirubinaemia predominantly conjugated with peak levels of

170-650 micromol/L is noted between two and ten days postoperatively. The levels of alkaline phosphatase are elevated two to fourfold, in contrast to transaminases, prothrombin time and albumin which are only mildly abnormal. This type of jaundice is self-limiting and uncomplicated in the vast majority of cases, clearing completely by the second or third week, provided other medical problems can be corrected or avoided. The diagnosis can usually be confidently made from the clinical picture alone. However, it is important to exclude postoperative cholestasis from extrahepatic biliary obstruction. An ERCP may be indicated to rule out extrahepatic obstruction. If further doubt exists, a liver biopsy, though nonspecific, may be helpful, revealing cholestasis and few or no signs of hepatocellular necrosis or inflammation.

Viral Hepatitis

Postoperative viral hepatitis is not a common problem in the immediate postoperative period. Transfusions of blood and blood products may cause viral hepatitis, but the incubation period is usually six weeks to six months following transfusion. In rare instances the incubation period may be as short as two to three weeks. Hepatitis B and non-A non-B viruses as well as the delta agent are implicated in posttransfusion hepatitis. Hepatitis A virus does not appear to be a problem from transfused blood. The relatively uncommon causes of viral hepatitis in the postoperative period are cytomegalovirus and infectious mononucleosis. These typically occur three to eight-weeks after extracorporal circulation. Serological tests are available to establish the various causes.

Postoperative Jaundice in Patients with Pre-Existing Liver Disease

Patients with pre-existing liver disease are generally at high risk for the development of postoperative jaundice. This is particularly true of patients with cirrhosis who undergo surgery for portal hypertension. The postoperative course in the cirrhotic patient may be further complicated by ascites, renal failure, encephalopathy or haemorrhagic problems.

The diagnosis of acute viral hepatitis should be considered a relatively serious contraindication to surgery except in life-threatening situations. Surgery in patients with acute or subacute viral hepatitis is attended by an unacceptably high postoperative mortality rate.

When a patient with known liver disease requires surgery, special attention should be given to careful preoperative correction of anaemia, hypoprothrombinaemia, hypoalbuminaemia and electrolyte disturbances. Hypotension and hypoxaemia should be avoided. There is no evidence that halothane anaesthesia is more dangerous in the patient with pre-existing liver disease or in patients undergoing biliary tract surgery. Many anaesthetists avoid its use in these patients, however, because of the potential difficulty in interpreting changes in liver function tests in the postoperative period.

Postoperative Jaundice Due to Extrahepatic Biliary Tract Obstruction

Obstruction of the extrahepatic biliary tree is a rare cause of postoperative jaundice, but is none the less important because surgical exploration is usually required. Postoperative intrahepatic cholestasis can easily be confused with bile-duct obstruction; judicious use of ultrasonography and cholangiography (ERC, PTC) is important to confirm extrahepatic

obstruction.

Bile-duct injury may occur during cholecystectomy, common bile duct exploration, other operations in the upper abdomen or as a result of extensive trauma. The injury is often unrecognized at operation and manifests itself in the early postoperative period with jaundice, biliary fistula or bile peritonitis. Cholangitis and formation of subphrenic or subhepatic abscesses are common complications. Early surgical re-exploration and appropriate management of the injury to the biliary system are usually necessary to avoid the effects of continued cholangitis and further damage to the liver.

Choledocholithiasis (common bile duct stones) usually present as persistent jaundice following cholecystectomy or common bile duct exploration.

Acute postoperative pancreatitis is an infrequent complication of abdominal surgery and a rare problem in surgery involving areas remote from the pancreas. Jaundice develops in approximately 30% of patients. The jaundice, usually low grade, results from edema of the head of the pancreas, causing obstruction of the intrapancreatic portion of the common bile duct. The diagnosis is suggested by elevated serum and urinary amylase levels and the management consists of the usual measures for acute pancreatitis.

Miscellaneous Causes of Postoperative Jaundice

Postoperative acute cholecystitis is an uncommon but increasingly recognized problem, often presenting as jaundice within the first few weeks after surgery. The onset of cholecystitis is heralded by anorexia, vomiting, abdominal distension, fever, right upper quadrant pain and tenderness, and a neutrophil leukocytosis.

Liver-function abnormalities include mild elevations of the transaminases and alkaline phosphatase, and variable elevations of bilirubin, which rarely exceed 85 micromol/L.

The pathogenesis of the cholecystitis is complex. Acalculous cholecystitis occurs inj more than 50% of cases. Increased viscosity of bile due to dehydration, fasting, narcotic analgesics and intravenous nutrition results in functional gallbladder outlet obstruction and increased intraluminal pressure. Hypotension, the use of vasopressor drugs, increased intraluminal pressure and thrombosis of the blood vessels in the gallbladder wall result in mucosal ischaemia and necrosis. Secondary bacterial invasion may occur. The mechanism of jaundice in this condition is probably due to functional obstruction of the common bile duct.

The diagnosis of cholecystitis in the postoperative period is characteristically difficult. Ultrasonography may demonstrate the presence of stones and sludge, thickening of the gallbladder wall and dilatation. Radionuclide hepatobiliary scintigraphy with 99mTc-IDA compounds may indicate non-filling of the gallbladder. A high percentage of these patients develop gangrene and perforation of the gallbladder; early surgical intervention is indicated if the diagnosis is likely.

Inherited Disorders of Bilirubin Metabolism

Both Gilbert's syndrome and the Dubin-Johnson syndrome are frequently diagnosed after a surgical procedure. Gilbert's syndrome is a benign inherited condition in which the patient has a slight elevated unconjugated bilirubin level in the 25-50 micromol/L range. Other liver-function tests are normal. Liver histological findings are normal and there is no evidence of haemolysis. There is a diminished capacity to clear bilirubin from the blood, with a reduced amount of the hepatic conjugation enzyme, glucuronyl transferase. The Dubin-Johnson syndrome is characterized by both unconjugated and conjugated hyperbilirubinaemia and the presence in the liver of a melanin-like pigment. Other liver-function tests are normal and the principle defect is a reduced capacity to transport organic ions into the bile from the hepatocyte. In both these syndromes fasting, stress and mild infections often cause the bilirubin to rise and become clinically evident. The key to the diagnosis is the return of the bilirubin to its slightly elevated preoperative level with the resumption of feeding and control of infection. Both are benign and require no treatment.

Total Parenteral Nutrition and Hepatic Dysfunction

Reversible mild abnormalities in liver-function tests are common in patients on total parenteral nutrition (TPN). These include non-specific mild elevations of transaminases, glutamyltransferase and alkaline phosphatase. Jaundice in adults is rarely attributable solely to TPN. The mild hepatic dysfunction may be related to fatty infiltration of the liver as a result of carbohydrate overload, essential fatty acid deficiency, folate deficiency or fat overload syndrome. It is, however, more commonly related to the underlying and associated conditions.

Comment

Postoperative Jaundice

G. A. G. Decker

From a practical point of view it is important to separate postoperative jaundice which occurs following operations in the immediate vicinity of the common bile duct from that which occurs following operations in which there is no possibility of the common bile duct having been damaged. In the latter case the surgeon can approach the jaundice problem with what amounts to clinical detachment once postoperative cholecystitis has been excluded.

Damage to the common bile duct during a cholecystectomy can be avoided if a prograde (fundus to cystic duct) dissection is done. There is considerable debate about the indications for operative cholangiography, but I believe that a surgeon in training should do this investigation with every cholecystectomy. The surgeon must be able to demonstrate the junction of the cystic duct with the common bile duct to his assistant. Accessory bile ducts running between gallbladder and the liver are a cause of unexpected bile drainage after cholecystectomy. I always place a dry swab in the gallbladder bed and look for bile staining of the swab which would inhdicate division of an accessory duct. I have not been able to demonstrate an accessory duct by this method. The only reasonable explanation is that there is minimal production of bile during anaesthesia. When there is excessive bile drainage post-

cholecystectomy it is reassuring tio be able to show the operative cholangiogram to one's colleagues and so allay their unspoken fears.

When I operate on a jaundiced patient I do a Trucut biopsy of the liver or excise a small piece of liver tissue from the inferior border if the liver is in any way abnormal macroscopically. The liver histology may help in the evaluation of the postoperative jaundice.

Jaundice invariably occurs after partial hepatectomy. It is usually mild and is due to retention of conjugated bilirubin. The alkaline phosphatase may rise to high levels in the recovery phase. The hyperbilirubinemia is probably due to a combination of hepatocellular damage, haemolysis of transfused blood and liver ischaemia.

It is also possible to damage the common bile duct when dissecting the duodenum during a Billroth 2 gastrectomy. There is little risk of damage to the common bile duct provided the surgeon confines the dissection to the duodenal wall by dividing only small bites of tissue between the duodenum and the head of the pancreas.

The presence of bile in the nasogastric aspirate, bile pigments in the stool and both urobilin and bilirubin in the urine exclude a complete intra- or extrahepatic obstruction. There is a tendency to overlook these simple tests and resort to expensive biochemical tests and ultrasonography in the first instance. The trite phrase that ultrasonography is operator dependent is an euphemism for saying that there are good and bad ultrasonographers. Ultrasonography is no substitute for a careful clinical evaluation and examination of the patient.

In patients in whom extrahepatic obstruction has been ruled out there is often a combination of factors responsible for the jaundice. Provided the patient's progress is satisfactory the bilirubin, alkaline phosphatase and liver enzymes are monitored twice weekly. The patient's jaundice invariably improves without the exact cause having been pinpointed.

Hepatitis B virus infection occurs uncommonly after blood transfusion. Non-A and non-B hepatitis is now the most common cause of posttransfusion hepatitis.

Comment

Postoperative Jaundice

P. Bauling

The authors point out a variety of important factors that influence hepatic blood flow during trauma, shock or sepsis. A parallel may be drawn between the intrarenal vasoconstrictive events induced by circulatory insufficiency and aggravated by other vaso-active substances, ultimately leading to renal impairment or high-output renal failure. Just as in the case of the kidney the surgeon must be aware of these perfusion alterations that may occur in the liver and take every possible step to prevent them.

The surgeon must view it as his responsibility to remind the anaesthetist of recent halothene anaesthesia in patients who are to undergo multiple surgical procedures.

Once again recent literature has emphasized the exceptionally high mortality in patients with pre-existing portal hypertension undergoing unrelated surgery. Therefore, the patient with existing liver disease, particularly portal hypertension, should be very carefully assessed if and when any form of surgery is contemplated.

Technetium 99 HIDA scan is not always reliable in diagnosing acute acalculous cholecystitis in a postoperative patient, therefore the clinical index of suspicion should always remain high.

Chapter 3.15: Multiple-Systems Failures in the Critically Injured Patient

G. W. Geelhoed

Introduction

A group of "new diseases" is being discovered in the management of critically injured patients. The discovery of these organ system failures had come about from protracting the components of natural processes long enough to identify the components distinctly, and to define their interrelationships.

Death is a natural process that all living creatures pass through. Death may be described at the level of the organism, or the organ system, or the cells of which these organs are composed as each of these units and subunits loses function. Shock has been called the "pause on the road to death". Shock is the final common pathway through which a variety of environmental impacts and inner-organ failures affect the organism as each vital organ begins to die a little at a time. A critical point is reached when the insufficiency of each organ system adds up to the collapse of the entire organism made up of these component parts. This process may proceed rapidly, as when circulation stops, and the physician has time to recognize only changes at the "macro" level. But with recent wide-spread application of effective therapeutic techniques for general support, each step in this sequence can be protracted, and a finer focus can be drawn on sequentially failing organ systems.

Failing Organs in a Failing Organism

The response of the intact organism in shock has been recorded in a number of observations. Death is defined for most organisms as the instant of collective failure of vital organ systems. There are, however, differences in different organs' susceptibility to decreased nutrient flow and hypoxia. Each organ system does not deteriorate at the same rate in shock, and similarly, there is a difference in the responsiveness of each organ system to the effectiveness of therapy. Our semi-successes in resuscitation have resulted in a number of "shock syndromes". The post-shock syndrome is usually labelled by the name of the organ which got "stuck" in failure during recovery of the less refractory organ systems. The post-shock syndromes also typically involve the organ failures for which we have no effective substitute. As seen in table 3.15.1, the evolution of these post-shock sequelae retraces the steps in evolution of techniques in trauma management.

Trauma is endemic in mechanized societies in which things and persons are moved at high velocity. Personal injury may result from deceleration of the body, or of missiles

stopped by the body, resulting in blunt or penetrating multiple trauma. These focal injuries may produce lesions in one anatomic region of the body followed by sequentially failing organ systems in other parts of the body quite remote from the site of the original injury. It is this paradox that we wish to examine, i.e. that previously active individuals sustain traumatic injury and often succum to organ failures seemingly unrelated to the original trauma.

Synergism and Organ Reserves

Some patients with previous health limitations, such as the old or those debilitated by disease, do not seem to pass through a sequential failure process, but apparently die of the primary injury. These patients are said to have limited reserves, or compromised tolerance. The concept of an organ system's reserves is important in understanding the multiple organ-failure syndromes. If the function of one organ system is lost, other systems in the body can partially compensate for that, only at the cost of expanding their function and using up reserve capacity. For example, some organ insufficiencies can be partially compensated for by increasing delivery of nutrients, even if in lesser concentrations, by augmenting cardiac output. In some circumstances there are insufficient reserves for this compensation to be effective; for example, some patients with chronic pulmonary insufficiency may decompensate under stress when cor pulmonale develops - that is, the heart is the final failure in using up its reserves to make up for the deficiency in the lungs. Patients with a combined problem called the hepatorenal syndrome show the interrelationship of these organ systems so that one insufficiency can be present and the patient will still get by through the means of borrowing against the reserves of another. But when these reserves are used up, decompensation occurs in both systems. Every clinician is familiar with the treatment of patients in whom things appear to be going well for a time, and then with a crescendo cascade, one system after another fails in rapid sequence as the synergism spirals out of control.

Organ Substitution and the Definition of Human Life

Physicians can now replace artifically the functions of some failed organs. With one notable exception, we can efficiently substitute artificial means of ventilation, circulation and even have measures to enhance or replace most failing organ systems. When a patient is supported by these synthetic or borrowed life functions grafted from a donor, it is sometimes difficult to ascertain life within the patient. Although it may appear that life resides more in the machines that we use to support patients than in the people themselves, we have already noted that the natural synergism between organ systems makes it very difficult to support several failing organ systems simultaneously. And there is one single organ system whose function defines human life for which we currently have no effective substitute - the human brain. Consequently, our efforts at supporting and resuscitating patients will be designed to maintain human life, for which a functioning central nervous system is a prerequisite. When multiple sequential organ failures include the failure of the central nervous system, at that time we say that the death of the patient has occurred, and we do not persist in support or substitution of the other failing organ systems. Some organs may still be functionally useful after the death of the brain (that is, the patient) and some of these organs are suitable for transplantation to tranfer that function to other patients who lack that organ system's function. It is important to recognize not only our capabilities in managing the patient with support to failing organ systems, but also our limitation, so that we know when to quit, when to allocate

machines and resources to other individuals who have hope of recovery, and when to pass vital functions along the others who might benefit from these organs.

"Irreversible Shock"

One of the first organ failure syndromes described was incorrectly attributed to the organism rather than a failing organ subsystem. Investigators called this post-shock sequel irreversible shock. It was described in laboratory animals in experiments in which resuscitation was found to be efficacious under some circumstances when hypovolaemic shock was promptly treated. However, if volume restitution were delayed for any period, the organism would not survive even if full-volume therapy that would have been efficacious earlier in treatment, were given. Some critical turning point was presumed that applied to the intact organism beyond which shock was refractory, and life could not be sustained despite treatment.

Irreversible shock was a concept of nihilism - a state in which treatment could do no good and only prognosis could be assured. Now both the concept and the term irreversible shock are obsolete. The concept arose from misunderstanding of the differential sensitivity of the organism's component organ systems to shock stresses. As seen in figure 3.15.1, it was known that an organism could be revived by reconstituting the volume of blood shed if that happened within a period of several hours after the haemorrhage. However, if a protracted period of several more hours passed, the organism could not be saved by restoring blood volume alone. However, the heart is the first organ perfused by the heart - that is, the coronary arteries are the first branches of the aorta, and the heart shares in the ischaemic changes brought about when reduced blood flow is supplied to each organ system. Myocardial ischaemia decreases the cardiac reserves so that when blood volume is reconstituted, the heart can no longer make effective delivery of this restored volume in an adequate cardiac output. "Pump failure" results, and this variety of shock is compounded on the original hypovolaemic insult. Although treatment directed at the hypovolaemia can restore an effective blood volume, unless the superimposition of the cardiogenic shock is treated by therapy beyond that which is directed only at the hypovolaemia, survival cannot be achieved. However, when the pump failure is recognized as a sequel of the initial hypovolaemic shock, and cardiotonic drugs or cardiac support devices are employed in addition to volume therapy, irreversible shock can be reversed (fig. 3.15.1).

All shock is not reversible by combining volume therapy and cardiac support, since to presume that this therapy should be effective would be to overlook other combination of organ failures which may remain as late sequels of the primary injuries, even if blood volume and cardiac output are restored.

Acute Renal Failure

A further weak link in the chain of life is the kidney - a vital homeostatic organ system. One military surgeon in Worl War II made an observation that the kidney was the rate-limiting step in resuscitation of the wounded at that point in history: "A chain is only as strong as its weakest link. When links are strengthened where the chain has broken previously, new weak spots appear simply because the chain holds to test them. The obvious weak link in the severely wounded in this war was the kidney".

There are at least three reasons for the later evolution of acute renal failure as a post-shock syndrome. First, the kidney has an amazing ability to regulate its own perfusion during periods of decreased blood pressure and flow through a combination of neurohumoral mechanisms as seen in table 3.15.2. Over a wide range of pressures and flows, the kidney is able to autoregulate its resistance to keep its renal perfusion nearly constant. When blood pressure decreases below approximately 80 mm mean arterial pressure, the auto-regulatory resistance of the kidney is wide open and now at successive decreases in blood pressure, renal decreases in perfusion result. At that point the kidney still has the ability to release a hormone into the circulation which through its action in converting angiotensinogen into an active polypeptide called angiotensin, the kidney directly exerts a vasopressor effect within the circulation. The same vasoactive octapeptide, angiotensin II, generated as a result of renin release, is the stimulus to the release of aldosterone from the zona glomerulosa of the adrenal cortex, which results in volume expansion by salt and fluid retention. So, through the three mechanisms of autoregulation, direct vasopressor action, and indirect fluid volume expansion, the kidney is directly influenced by its own perfusion, retarding the effects of shock.

Table 3.15.2. Three-stage control of perfusion by renal regulation

1. Autoregulation of resistance

2. Vasopressor effect of renin (angiotensin) secretion

3. Volume expansion by salt and fluid retention.

The second reason that acute renal failure was a later discovery in the post-shock syndrome is that the organism is not dependent for minute-to-minute survival on renal function. This is not the case for several other vital perfusion circuits, such as the heart or the lungs where existence is determined beat by beat and breath by breath. Renal function can be lost completely and the organism can survive by employing compensatory mechanisms within other organ systems' reserves. For example, there can be respiratory compensation for acidosis that would normally have been managed by the kidneys. Respiratory compensation may be a temporary phenomenon only, however, since the mechanism of this compensation is to use up fixed reserves of buffer in the plasma, and to increase the respiratory rate within physiologic limits. The ultimate solution to acid-base imbalance in the post-shock patient with metabolic acidosis is the responsibility of the kidney, and without the kidney, only transient and inadequate compensation is possible when using reserves in the other organ systems.

A third reason for the later "discovery" of acute renal failure as a post-shock sequelae is that a method of substitution for renal function has been invented. An artificial device can be employed to substitute for some of, but not all, the renal functions that are lost in acute renal failure. The dialysis technique allows the physician to buy time to concentrate on the reserves of other organ systems and hopefully to await renal recovery. If the kidneys never recover and the patient goes on to develop end-stage renal disease, the temporizing technique of dialysis becomes chronic in long-term substitution for some of the kidney functions, but only if other organ systems have taken up the slack.

Stress Ulceration

The gut also suffers during hypoperfusion in shock, but unlike the kidney, the gut does not seem to compensate through regulatory mechanisms for the benefit of host homeostasis. With the shunting of blood away from the gastrointestinal tract in shock, autodigestion may occur resulting in ulceration or gastrointestinal bleeding, further compounding the stresses of the initial injury. The gastrointestinal tract is not an effective organ system for nutrient absorption during shock, and its decompensation may further compromise other vital organ systems such as inhibiting ventilation.

At the same time that additional energy resources are being mobilized for the preservation of the organism, the gut fails in its function of digestion and absorption for reconstituting of the fuel deficits within the systems that are expending their energy reserve. A substitute for this nutrient function is now available in the "artificial gut" represented by total parenteral nutrition. Supply of nutrients parenterally without relying on the gut conserves functional proteins in other organ systems' reserves from catabolism where they might be consumed for energy purposes only.

Shock Lung

Adult respiratory distress syndrome (ARDS) has entered the lexicon of intensive care units as resuscitation techniques allow acutely ill patients to survive longer and develop sequelae for which no treatment has yet evolved. Shock lung is a later sequel to evolve after injury, and, at least to some extent, it may be a result of treatment. Adult respiratory distress syndrome is also correlated with the presence of sepsis, which takes some time after injury to develop. Shock lung, like many of the other post-shock sequelae, is a reflection of our success in managing the earlier physiologic disruptions of shock, since patients who are intensively treated can survive to develop complications of pulmonary insufficiency and sepsis.

No single etiologic agent is known for the development of shock lung. Pulmonary edema is a common hallmark following the alveolar-capillary injury. A decrease in surfactant activity also leads to impaired compliance and a decrease in oxygen transport by the bloodstream is the end product of pulmonary insufficiency. The single most important measurable entity in shock lung is the physiologic shunt - that is, the proportion of lung that is perfused but not ventilated. This portion of lung is ineffective in adding oxygen to the bloodstream, and the decrease in oxygen saturation that results means that the vital organ perfusion beds must shift to anaerobic metabolism, an inefficient energy utilization system that further stresses reserves.

Management of the lungs in the post-shock state is a delicate balance between maintaining the oxygenation of the blood and minimizing injury to the lungs. At present there is no effective extra-pulmonary oxygenation device that can function practically for prolonged periods. This means that the maintenance of gas exchange at the cellular level must take place through careful increases in the rate, volume, pressures and oxygen tensions in the ventilated lungs. Since the lungs are the injured organs in the shock-lung syndrome, stressing the lungs to maintain the other systems in the body is the reverse of the usual policy of putting an injured part to rest to allow time for repair. The delicacy of the balance between appropriate

ventilation adequate to sustain life and further compounding the injury to the lungs makes shock-lung management a challenging experience which draws heavily on the reserves of the other organ systems which may be failing themselves. The fully fledged shock-lung syndrome is probably not successfully treatable, but recognition of the mechanisms of pulmonary insufficiency following shock allows its recognition and some therapeutic techniques applicable in its prevention.

Shock Liver

The liver is a complex parenchymal organ of excretion and secretion, playing major roles in host homeostasis through its digestive functions and synthesis of functional proteins and energy storage. Even under the best circumstances, hepatic perfusion is marginal for the complex functions it must perform, and following shock, the liver's capacity to perform these functions is severely impaired. Some descriptions of posttraumatic jaundice apply a specific name to the entity of post-shock hepatic insufficiency. However, many physicians caring for injured patients are familiar with the common phenomenon of posttraumatic jaundice or deficiency in clotting factors or other products of hepatic synthesis following major injury in other organ systems.

Adding to the problem of posttraumatic hepatic insufficiency is the increased load of breakdown products of blood and blood pigments, nitrogenous waste and other products of protein catabolism that follow major injury, particularly if accompanied by sepsis. In the very setting in which liver is called upon to perform extra functions in mobilizing its own reserve, its fundamental processes are impaired. This insufficiency shifts a burden of extra compensatory function to the reserves of other organ systems.

Central Nervous System Failure and Death

Central nerous system dysfunction is an early consequence of failures in other organ systems. Unconsciousness can result from direct closed or penetrating head injury from the original trauma, but can also follow from ischaemia or hypoxia of the central nervous system following insufficiency of respiration or perfusion of the brain.

As noted in the introduction, higher function in the central nervous system is a feature that is distinctive in human life. If irreversible loss of function occurs in cortical cerebration, "brain death" is said to have occurred. This term is a neologism that is incorrect from several points of view. Apart from the grammatical error of using a noun as an adjective, it implies that there are several kinds of death, and that there could be "gut death" or "heart death" as well. Teleologically, the purpose of all these other organ systems might be said to preserve the function of the central nervous system, which is necessary for the continuance of life. The importance of an adequate cardiac output of well-oxygenated blood is secondary to the primary purpose that central nervous system function be maintained. If the heart beats and the lungs oxygenate the blood delivered by the heart, these secondary functions are to no human purpose if central nervous system function has been totally lost.

For that reason, death of the central nervous system is certifiably equivalent to human death, and this criterion serves as the major indicator for the application of drugs and devices to support other failing organ systems or their withdrawal. The central nervous system

remains the *sine qua non* of the patient's life, and the absence of this function distinguishes living patients from potential organ donors. A number of sophisticated tests and criteria have been established to determine the point at which deterioration of the central nervous system crosses the boundary line of "brain death" so that allocation of patient support resources can be reserved for those patients for whom there remains hope of survival.

Multiple, Progressive or Sequential Systems Failure

Life is a steady state of a dynamic interrelationship of several organ systems. Insufficiency in one system is offset by borrowing against the reserves in another. When insufficiency develops in more than one of the organ systems, it becomes increasingly difficult to design therapy that will support one organ system without severely compromising another whose reserves may be already exhausted. Progressive organ failure may develop sequentially and planning strategies for management of the patient with these failing organ systems will shift in primary purpose over the course of time as well. At each point in the process, the therapeutic strategy would be to support these weakest link, favouring the most critical failing organ system, without borrowing too heavily against the reserves of the other organ systems whose function is already impaired.

The multiple-injured patient with several failing organ systems is described as a "critical" management problem, since every moment in his treatment is a crisis in which all the collective cells and organs are beginning an entropic collapse. As this death occurs over a protracted time, the physician has the opportunity to intervene in the events of this process by selectively supporting critical functions that will aid in achieving survival of the organism. To the extent that we are successful in applying any of these techniques, we will continue to be left with residual organ failures after restoration of functionin other organ systems, or in their substitution. The final human function for which complete substitution is not envisaged is that of the central nervous system, and defeat in the sequential organ failure systems occurs with the death of the brain. Until that ultimate event occurs, our "semi-successes" in resuscitation will continue to produce specific post-shock syndromes of isolated or combined organ system insufficiencies.

Comment

Multiple Systems Failure

C. J. Mieny

In this chapter a concept is put forward that the same process effects different organs at different times in a sequential manner - the weakest link or domino theory. In this theory, a patient with a major trauma and sepsis relying on mechanical or pharmacological support of a failing organ can now survive sufficiently long for another organ to fail.

What, though, are the common factors, the common final pathway of organ failure? It is likely that failure of the systems must start at the cellular or subcellular level in many organs and when a sufficient number of cells fail in one particular organ, that organ fails, and the next organ, and the next.

There seems to be common clinical factors in all these patients: a period of shock and cardio-vascular instability after injury, multiple blood transfusions and invasive sepsis. The insult seems to start at the cell membrane. The membrane's potential decreases, the NaK/ATPase system is activated and the high energy phosphate compound ATP is used. The mitochondria are stimulated, cyclic AMP decreases, sodium moves into the cell and the mitochondria and endoplasmic reticulum swell. This leads to decreased metabolic capability and eventually lysosome leakage and cellular destruction. When enough cells have been affected, the organ fails.

These changes are the result of shock with cardio-vascular instability, marginal ventilatory function, severe catabolism and a depressed immune response. It is usually relatively easy to support the patients with single-organ failure. Multiple system failure is a much more complex problem and mortality is high.

- Circulatory collapse requires volume replacement followed by inotropic agents, vas-active agents and sometimes intra-aortic balloon pump assistance.

- Ventilatory collapse requires a volume-cycle ventilator, diuresis, PEEP and sometimes extracorporeal oxygenation.

- Renal failure requires volume replacement, diuretics, dialysis early to get rid of fluid, potassium and the breakdown products of metabolism.

Metabolic failure is being recognized as a major factor responsible for multiple systems failure leading to mortality. It has been well shown by Clowes et al that one or more circulating agents are present in the blood plasma of septic patients which are capable of inducing muscle protein degradation and an accelerated rate of amino acid clearance. It has also become clear that agents produced by the immunological system, particularly by macrophages, may exert a significant stimulatory influence on both visceral protein synthesis and muscle protein degradation. Interleukin-1 (IL-1) induces hepatic synthesis of acute-phase reactive proteins and proteolysis in muscle. A very important proteolysis inducing factor (PIF), the active circulating cleavage product of IL-1, induces the accelerated protein synthesis necessary to support the humoral, phagocytic and cellular aspects of the immune system. A large number of proteins must be synthesized to satisfy the needs for immunocompetence, coagulation and preservation of organ function. In major injury, survival will depend on a series of integrated hyperdynamic physiologic and metabolic responses required to maintain energy production and cell function throughout the body.

The intestinal mucosa is among the tissues, with the liver, with the most rapid synthesis and turnover of amino acids. Depletion of amino acids after major injury results in atrophy of the mucosa and translocation of bacteria from the gut to the portal system contributing to liver injury.

The relationship between interleukin-1, proteolysis inducing factor and rapid protein synthesis seems to be an important link in the relationship between sepsis and multiple organ failure.

Chapter 3.16: Perioperative Management of the Child

J. H. R. Becker

Introduction

The perioperative management of the child is as important as the operation, and attention to detail by the surgeon performing the operation is usually taken for granted. However, the vital peroperative support is often neglected and it is usually only the natural resilience of the child to trauma that ensures healing; often the fact that the child survives the operation is the only criterium of success. Children should not be managed by untrained personnel or in facilities that are ill-equipped. The child with a surgical problem is not the same as and cannot be compared to the child with a medical problem who needs a bed, medicine and TLC. Surgery is often superimposed on an existing medical problem which, on its own, has morbidity and mortality. When an operation needs to be performed special considerations must be kept in mind, for example, the premature neonate that had a stressful birth will have all the problems of prematurity to cope with and if the baby develops necrotising enterocolitis needing a general anaesthetic, laparotomy and bowel resection, the surgeon must be able to manage not just the surgery, but also the underlying medical condition, preoperatively, intraoperatively and postoperatively.

The child with his growing anatomy, developing physiology, and a lifetime ahead of him, is entitled to ideal conditions of perioperative care and trained operators, not just somebody "who has done a lot of cases".

The Referring Colleague

This is where perioperative care starts and unnecessary complications should be anticipated and averted. An example of such a complication that will definitely affect the prognosis is the hypothermia sepsis and dehydration associated with a ruptured exomphtalos. However, in consultation with the paediatric surgeon, the referring colleague would make sure that the bowel is placed in a plastic bag, and in this way dehydration, sepsis and hypothermia would be prevented. An added bonus is that, with the bowel in a transparent cover it can easily be inspected, for strangulation.

Depending on the familiarity of the referring doctor or institution with care of the neonate, the paediatric surgeon will have to transfer a considerable amount of information by phone concerning precautions and essential that are needed, i.e. a neonate or child with an abdominal emergency needs nasogastric suction for adequate drainage, the smallest nasogastric tube used for gastric decompression is a size 8 French stomach tube, for older children bigger sizes should be used. If the attending doctor uses to small a tube, he may think that the baby's stomach has decompressed, but in fact the stomach has not decompressed completely and this can result in retching and aspiration.

A child that is NPO and is an emergency should have functioning IV line but, depending on the referring colleague's proficiency in treating newborn babies in particular, it might be better to transfer before attempting for hours to get an IV going. All the good veins may be perforated during these attempts and that would necessitate a more drastic

procedure for venous access at a later stage. The only absolute indications for an IV line in a newborn are a perforated exomphalos, gastroschiseis, a delay in transfer, correction of an existing deficit or anticipated ongoing fluid loss. In the older child venous access does not usually pose many problems. Virtually every emergency that needs transfer to a paediatric surgery unit needs some attention paid to details pertaining to the treatment of the condition, so the paediatric surgeon should be consulted on all aspects of the initial care prior to transport.

The Following Information Must Accompany the Transfer

- Maternal and family history of congenital abnormalities.

- Quality and duration of the pregnancy, eclampsia or hydramnios.

- Labour (3 stages), i.e. prolonged rupture of membranes, APGAR of the baby, instruments used to assist the labout and even the presentation of the baby.

- Written consent to perform an operation unless the father accompanies the patient.

- All special investigations to date, for example:

    - X-Ray films

    - Sonar

    - Blood gasses

    - Serum electrolytes

    - Serum glucose

- A specimen of maternal blood

- Details of all treatment to date.

Transport

Transportation is often left to an untrained ambulance driver and a junior nurse, the baby arrives at its destination hypothermic and with the drip in the tissues. It is vital that the baby is transported with the utmost care. As a principle the more severe the underlying condition is, the more senior and experienced should the accompanying person be. No-one should consider himself to be too important or too senior to accompany a patient.

Temperature

There are certain important considerations to be borne in mind during transportation of a neonate. As the neonate cannot maintain its own body temperature, precautionary measures have to be taken to prevent abnormal losses and to supply external heat. The

neonate loses body heat very easily owing to a number of factors. His body surface area is large in relation to his body mass, if this large area is exposed to an unfavourable environment, body heat is lost and the relatively smaller mass cannot generate enough heat to regulate his own temperature. The rapid loss of heat through the skin is a result of the very thin stratum corneum of the skin, which means that the subcutaneous capillaries are very close to the surface and thus conducts heat to the environment. Another contributing factors is the neonate's rapid breathing resulting in a loss of body heat in the warm, exhaled air. Although the neonate's metabolic rate is double that of an adult, he cannot supply enough heat to compensate for the abnormal losses. Endogenous heat production is usually not enough to maintain body temperature. Abnormal losses can be avoided by wrapping the baby in aluminium foil, which has a "thermos flask" effect, and by placing it in a functioning incubator, which is a good external heat source.

Respiration

An open airway is imperative under all circumstances. The baby has special problems because of the small size of his larynx and trachea. The slightest obstruction due to mucous or oedema could be fatal. It is hazardous to intubate during transportation owing to the possible inexperience of the personnel, the limited space in the incubator and ambulance, and the movement of the vehicle. En route monitoring of oxygenation and respiration is difficult, making the decision whether to intubate en route or not, harder. The decision to intubate and ventilate the baby or child should be made before transportation, while all the conditions are optimal and the least harm can be done.

Position of the Child

Whether the child should be prone or supine depends entirely on the underlying condition, for example the baby with an oesophageal atresia and distal trachea-oesophageal fistula is susceptible to the aspiration of gastric contents if nursed supine. By nursing the child in a prone position at an angle of 30-45 degrees, the chances of aspiration are reduced. Thus a complication that can seriously affect prognosis can be averted.

Mode of Transport

Whether transport is by ambulance, private car or by air depends entirely on what is available, the urgency or the distance. For example, a Bochdalek hernia with respiratory distress will need evacuation by air and an uncomplicated irreducible hernia can be transported by car or ambulance.

Accompanying Person

As a general principle the person who accompanies the patient should be qualified to manage any expected problems that might arise, for example, a ruptured exomphalos or a Bochdalek hernia that is being ventilated needs nobody less than a doctor. A qualified sister can accompany the patient with a bowel atresia and the parents can safely accompany the child who has an uncomplicated, irreducible inguinal hernia.

Care on Admission

Besides attending to the basic pathology and reason for admission, the following procedures need immediate attention:

- Thorough evaluation of the baby - vital signs, temperature, pulse, respiration, hydration and other routine parameters.

- Airway management - make sure that no debris has accumulated en route.

- A neutral thermal environment is necessary to prevent abnormal losses and to supply the necessary external heat for temperature maintenance.

- Functional IV line - if there is one *in situ*, check that it is functional, if not, get one going.

- Cardiovascular monitoring - this is essential so that effective circulation is maintained, i.e. precordial ECG monitor or a peripheral pulse oxymeter.

- Laboratory evaluation - the following tests should be done:

    - Bloodgases

    - Urea and electrolytes (Na+, K+, Cl-, Ca++)

    - Haematocrit

    - Billirubin

    - Prothrombin index

    - Blood glucose

- Screening - additonal X-ray studies in conjunction with what has been done by the referring hospital or doctor.

- Sepsis can be prevented and treated by administering appropriate antibiotics.

- An arterial line should be placed *in situ* in all serious cases where constant monitoring of haemodynamic changes is needed.

The neonate or child needing emergency surgery has now been thoroughly evaluated and can be taken to the operation room.

Admission for an Elective Procedure

With an elective procedure everything has to be optimal, no complications can be afforded. The timing of the operation should be ideal, all special investigations must be

completed and the child should be in the best possible physical condition. To lose a child or to have a routine operation result in permanent brain damage due to something that could have been avoided, is unpardonable.

Vital Questions that Need to be Considered Before an Elective Procedure

- Does the child need the operation or can it be safely postponed?

- Are there any contraindications for surgery, such as:

    - a cold or flu (wait 2-3 weeks for complete recovery after any infection)

    - anaemia

    - a cough

    - diarrhoea

    - fever - a complete diagnostic workup needs to be done to establish the cause

    - negative protein balance - a positive protein balance is essential for healing to take place.

Essentials for Successful Surgery

- The patient should be in as optimal a state of health as his condition allows.

- The indications must be carefully weighed up and the correct operation for the pathology must be performed.

- There should be appropriate facilities for paediatric surgery.

- A paediatric anaesthetist (not a person who has handled many cases, but who has also had the appropriate training) should be available to administer the anaesthetic.

- A suitably qualified paediatric surgeon should perform the operation.

Hospital Orientation Programme

The whole operation and all its implications are often discussed at length with the patents without taking the child into account. He is never told what is going to happen to him or why he is to be hospitalized. The child's understanding should never be underestimated by trying to create a false impression that going to hospital is going to be fun, nothing is going to hurt him and in other ways by trying to shield him from the facts of the matter. The adults will not succeed in duping the child, but will only undermine his trust in them.

The child's fear of the unknown can be most amicably alleviated by preparing him adequately for hospital. The orientation programme should prepare him for the foreign

environment which he is going to enter. All the procedures which he will undergo or witness during his sojourn in hospital can be explained in his terminology by means of puppet shows, a slide show, tapes, videos, scrap books and hands-on experience with syringes, masks and other safe apparatus. Communication with the child at his level is a most important adjunct to the perioperative treatment of the young patient.

Premedication

This is vitally important. No child should enter theatre screaming or being torn away from a distraught mother. It is virtually impossible to get an IV line going, or do anything else for that matter, on a child who refuses to lie down. The adrenalin released causes a sympathetic response which is not needed at this stage.

A suitably administered premedication should sedate the child sufficiently to allow for calm transportation to the theatre and the induction of anaesthetic with a minimum response from the child.

If it is at all practical the theatre sister should also go the day before to the ward to introduce herslef to the child. When the child enters the theatre well-sedated but not asleep, masks should not be worn by the theatre staff, making the environment less hostile. The masks can be replaced as soon as the child is asleep.

Appropriate Theatre Facilities

The average general hospital theatre caters mainly for adults. Because of the special needs of the child, certain adaptations have to be made when a child or neonate needs an operation.

Theatre Environmental Temperature

In the average theatre the temperature is usually set for the comfort of the surgeon and staff, whereas in the paediatric situation the environmental temperature should be set to suit the patient and not the staff. An environment should therefore be created around the patient that will meet the needs of temperature regulation. There are a number of ways of regulating body temperature.

Heated Mattress

This is a heat source from below. There are two types available, hot water circulared or an electrical pad. Hazards with these appliances are overheating, burning or electrocution.

Babies especially are totally exposed while the team prepares everything for the anaesthetic and monitoring of the patient, i.e. arterial and venous access, catheters and intubation. All these procedure can take some time, during which a considerable loss of body temperature takes place. The overhead heater provides an environment wherein these procedures can take place without negatively affecting the child.

All liquids crystalloid or colloid that are going to be administered IV need to be

heated to body temperature. This can very easily be done by submerging the IV fluids in a bucket of warm water (approximately 37 °C). Do not overheat any fluids, especially blood products.

Drapes

A neonate needs to have warm circumferential cottonwool around his limbs and head, this prevents excessive loss of heat (fig. 3.16.3).

All the sterile drapes that are going to be used need prior heating in the autoclave. Be careful not to take them out of the autoclave too soon, because it is often difficult to judge exactly how long it is going to take before the baby will be ready for draping and they will be cold by the time you need them.

As a general principle, absolutely everything that is going to be used on the child, from the anaesthetic gas (fig. 3.16.4) to the drapes, need to be warmed to body temperature. However, just warming everything is not enough and an external heat source is necessary throughout the operation, such as an overhead heater or warming blanket.

Usually during preping of the abdominal wound or when the abdomen is irrigated with saline solution, some of the fluid collects underneath the baby, resulting in unnecessary cooling. This can be prevented by putting a large adhesive dressing over the abdomen with a hole cut out in the area of the wound. The adhesive dressing prevents the cottonwool from getting wet and besides keeping the baby dry, the plastic conserves the heat from the mattress around the baby. The above precaution is only necessary in neonates.

Antiseptic and Irrigation Solutions

As with all the solutions, these also need to be heated to body temperature. The same container that is used to heat the IV fluids can be used for these fluids.

Intravenous Line

The line must be functional (free-running when opened), it must be well secured and accessible to the anaesthetist. There is nothing more irritating to the surgeon and hazardous to the patient and the sterility of the wound, than an anaesthetist trying to get hold of an inaccessible IV line, or trying to get one functional while the operation is in progress. The number and calibre of the lines depend on the extent of the operation and the anticipated need for colloid and crystalloid.

When venous access is suddenly lost during the operation, in small babies and neonates, the umbilical vein can usually be catheterised by the surgeon via the laparotomy wound. This gives ample temporary venous access. This catheter should not be left *in situ* for longer than 24 hours, because it may cause portal vein thrombosis.

Caveat

No adult IV transfusion set is ever used on babies even though "it can always be set at a slower rate". A paediatric-giving set is always used "in line" with a buratrol or pedatrol, the latter never containing more fluid at any given time than the baby can receive in one hour. This safety measure is necessary to prevent the baby or child from being overtransfused.

Lighting

Three lights are needed:

- The large overhead operating theatre light

- A similar overhead light that shines onto the head of the baby. The anaesthetist can now observe the tubing and pallor of the child

- A headlamp - because of the small size of the wound in relation to the surgeon's hands and thenon-translucent heads hovering between the overhead theatre light and the wound, very little actually reaches the site where it is needed. For this reason a headlamp should be used during the operation, in addition to the large overhead operating theatre light.

Monitoring

No child should be given a general anaesthetic without the necessary monitors. The number of monitors (i.e. ECG, CVP, arterial line, urinary catheter) will vary depending on the size of the operation, but the absolute minimum is an ECG. No child should receive a general anaesthetic without at least an ECG monitor and an IV line. No surgeon should operate without these minimum requirements.

Core Temperature Monitoring

The probe can be placed orally or rectally. Maintaining a normal core temperature is absolutely essential for the metabolism of anaesthetic drugs and for the maintenance of normal cellular physiology.

The normothermic neonate responds to hypoxia by increasing the rate of ventilation, this response is absent during hypothermia. With the continuous monitoring of the core temperature hyperthermia or hypothermia can easily be recognised and the appropriate action can be taken.

Immediate Postoperative Care

The moment the final dressings are on the wound, the drapes are removed and the baby wakes up. The overhead heater should be switched on, because the child is going to be exposed so that the anaesthetist can observe respiration, tone, perfusion and oxygenation.

Transport from Theatre to the Recovery Room or Even to Intensive Care

It is amsolutely useless to accompany any neonate or child to the recovery room or to observe the child if you do not take the laryngoscope and tube with you.

The endotracheal tube that was used, or an exact duplicate as well as a functional laryngoscope must at all times accompany the child until he is fully awake or until the surgeon or anaesthetist's responsibility has been handed over to another responsible person. It is preferable to use the laryngoscope which was used in theatre to intubate and extubate the child because you are sure that you can intubate with that blade and that the light and batteries are functional. It is hazardous to have a respiratory problem in the lift, passage or even in the recovery room with no equipment readily available. The average recovery room is usually geared for adults and not for babies or children and this must always be borne in mind.

Immediate Postoperative Care in the Ward

Any child or neonate that has had a general aneasthetic, regardless of the size of the operation, should be very closely monitored in the ward. The neonate might even need a precordial ECG monitor until he is fully awake, normothermic and breathing normally, even after a minor operation. To lose a child after an operation, regardless of how small or big, owing to poor monitoring, is unforgivable.

A neonate after a hernia repair might need close surveillance and precordial monitoring. Soon afterwards he will be fully awake and should be given a bottle to drink. Do not let the neonate or a child's ability to recover with remarkable ease and rapidity deter you from absolute vigilance in the early postoperative phase.

Last but not least, after the operation, regardless of how trivial or serious, at whatever time of day or night, communicate with the parents, preferably face to face, but if that is not possible, by telephone. Explain to them exactly what you have done, the prognosis and future procedures.

Your success in treating children will be directly proportional to your love for them, and your attention to detail even if you are a good surgeon technically. If you do not love children, leave them for someone who does.

Comment

Perioperative Management of the Child

H. Rode

Introduction

Between 75% and 80% of all surgery performed on infants and children is done close to their homes, usually in general hospitals and by surgeons who spend most of their time with adults. It is therefore essential that the basic perioperative management principles be

well-understood by all surgeons.

In comparison to adults, infants and children have unique morphological and physiological difference which profoundly influence their perioperative management. Outstanding characters are:

- the adaptations required for extrauterine life

- the rapidity with which life processes proceed and physiological changes

- organ immaturity and insufficiency (respiratory, renal, hepatic)

- demands imposed upon the child for normal growth and development

- the absence of acquired or degenerative diseases

- a resiliten cardiovascular system

- rapid postoperative recovery and the relative small size of the paediatric patient.

Serious physiologic limitations may also adversely affect the chances of survival, viz. major associated cogenital abnormalities, poor tolerance to stress and specific physiologic considerations of the preterm and small-for-gestational-age patients, i.e. hypoxia, hypothermia, hypovolaemia, hypoglycaemia, hypocalcaemia, hypoprothrombinaemia and anaemia. Other contributing factors are nutritional problems, hyperbilirubinaemia, oxygen toxicity, coagulation disorders, hyaline membrane disease, apnoeic attacks and polycythaemia.

Principles of Successful Perioperative Management in Children

NB: Treatment takes precedence over diagnosis and evaluation:

- Early recognition of surgical conditions

- Appropriate investigations

- Complete perioperative care

- Assessment of physiologic derangement

- Precision of fluid replacement

- Support failing organ systems

- Appropriate medication

- Constant monitoring

- Correct surgical procedure

The perioperative management of children can be divided into three main overlapping and integrated phases. It is however fortunate that immediate surgical procedures are seldom required in children without prior resuscitation. The three phases are:

- Preparation of the child for surgery

- Intraoperative care

- Postoperative care

Preparation of the Child for Surgery

Appropriate Surgical Centres

These are essential for optimum care although many pediatric surgical procedures are done outside these centres with good results. The following are basic requirements:

- Appropriately trained personnel

- ICU and laboratory facilities

Transport

Determine the transportability of the child. General principles are laid down, but if it unacceptable to transfer very sick unstable children until their condition has been stabilized. No amount of intensive care can reverse the damage done by hypoxia, hypothermia and hypoglycaemia. In essence, the objectives of transport are to provide a safe, warm environment, to ensure adequate ventilation with sufficient oxygen, (may need endotracheal intubation), appropriate fluid therapy, and nasogastric decompression (Reprogle tube). Respiratory failure is the most serious problem encountered during transportation. It is often advisable to discontinue intravenous therapy, if not absolutely necessary, for the duration of travel. The basis for safe transportation therefore is to maintain the baby in a good condition.

Care on Admission

The aim is to:

- Establish the diagnosis through history, physical examination and investigations (base-line, specific). Knowledge of preexisting medical problems will facilitate proper management from the onset. Preexisting cardiac, metabolic and renal diseases may be contributing factors in a child's response to therapy and may necessitate other pharmacological agents.

- Start resuscitation when indicated

- Correct the disease process through surgery or other therapeutic modalities

Although it may not always be possible to have full correction of all derangements,

every effort should be made to restore oxygenation and tissue perfusion by ensuring adequate ventilation, restoration of blood volume (see Table 3.16.1) and haemoglobin (minimum 10 g/dL) acid base and electrolyte disturbances, coagulation abnormalities (vitamin K1, FFP platelets) and antibiotics. The objectives of preoperative preparations are to minimize the risk of the anaesthesia and the operation and hence to improve outcome. The urgency and methodsw will be determined by the underlying condition.

Special Problems

Many homeostatic and biochemical derangements are age and disease related. These problems seldom occur in isolation and may be the first sign of impending disaster. Abnormal laboratory findings, however, should always be confirmed. Some of these common problems encountered are: hypoglycaemia, hypcalcaemia and hyperbilirubinaemia.

Acid-Base Balance

Infants, especially preterm and small-for-date babies are prone to acidosis, which is aggravated by infection, poor perfusion states and the trauma of surgery. Treatment is aimed at the primary cause, adequate fluid therapy and bicarbonate infusion.

Urine

The urine must always be tested for glucose, proteins, blood, osmolality and if urinary tract infection is suspected microscopy and culture should be done.

Antibiotics

Many surgical procedures have come to grief because of subsequent sepsis and special precautions are therefore warranted, i.e. regular handwashing and meticulous aseptic techniques during surgery and the establishment of vascular access. The choice of antibiotics is guided by the pathological problem. Generally, prophylactic antibiotics are used when the risk of infection if high, when contamination will occur, when the consequence of infection may be serious and in the compromised host. Prophylactic antibiotics are usually given within 6 hours of the surgical procedure or on induction of anaesthesia and continued for 48 hours.

Therapeutic antibiotics are given in established sepsis and then usually for 5-7 days. Broad-spectrum antibiotics are preferred. Penicillin, aminoglycoside and metronidazole are effective against most organisms likely to cause infections in surgical patients. Effective antibiotic serum levels should be confirmed with MIC and MBC levels. Fungal infections are not infrequently seen in children and mycostatin should be used judicially.

Drug Metabolism

Infants and children are exposed to large numbers of drugs for short or long periods. The pharmacological handling thereof will depend on the gestational and postnatal age of the patient, drug metabolism, excretion and specific drug characteristics. In general terms by the age of 2-3 years, drug absorption and elimination are equal to adult pharmacodynamics. Regular serum drug levels are important to ensure adequate administration. Of particular

importance is digoxin, certain antibiotics (gentamycin) and furosemide. Drugs must therefore only be given for specific indications.

Major System Diseases

Diseases such as asthma, diabetes, and cardiac failure must be adequately treated in the perioperative period. Hospitalization may be required for the insulin independent juvenile diabetic patient. However, when well-controlled with the judicious use of antibiotics, fluids and electrolytes and insulin administration, postoperative morbidity is very low.

Steroid Therapy

Steroid cover should be given to any child who has had steroid therapy for a period of more than 10 days during the three months preceeding surgery. This includes children who were on long-term topical therapy. Additional steroid therapy is not required if the children were not given steroids within three months preceding surgery. Careful observation of the child however is required during the perioperative period.

Premedication

Abdominal examination may be difficult in young frightened children and it may at times best be done under mild sedation provided that the child is not severely injured or has a head injury.

Solid intake is stopped 6 hours before surgery and clear fluids given by mouth 4 hours before scheduled surgery.

Drugs: Trimeprazine 3-4 mg/kg/dose - maximum 90 mg plus droperidol 0.2 mg/kg/dose maximum 5 mg.

Given 2 hours preoperative.

Given only to infants older than 8 months.

Consent for Surgery - Why, How, When?

Informed consent is a legal requirement before any surgery can be performed, but also helps to instil confidence and eliminate fear. The parents must always be part of the decisionmaking team and the following is required:

- Reasons for doing the operation

- Clear explanation of the procedure

- Alternative methods of treatment

- Possible complications

- Possible short-term/long term outcome

Operative Risks

The operative risk varies according to the disease process, the general condition and response to resuscitation, the age of the infant or child and the expertise and facilities available for treatment. All these factors must be considered when a course of therapy is being contemplated.

Timing of an Operation

It is fortunate that immediate surgical procedures are seldom necessary in children and the best time for surgery will be determined by the surgical disease and the patient's condition. Surgery can either be done for:

Emergency - life-threatening conditions (ruptured exomphalos, midgut volvulus). Resuscitation is often done in theatre and because of urgency, deficiencies are often only partially corrected.

Urgent - (appendicitis) needs full work-up and resuscitation.

Elective - (UDT) usually only done when the child is healthy and thriving and with minimal anaesthetic risk.

Intraoperative Period

Contrary to general belief, children and especially neonates tolerate surgery very well provided their special needs, physiologic limitations and disease processes are duly taken into account. The intraoperative period needs a team approach with no real territorial boundaries. A skilled anaesthetist is essential for safe anaesthesia.

The following are standard procedures:

- Check for correct and consent for surgery

- Placing the infant on the operating table. The infant or child is wheeled to the operating table in his incubator or trolley. The operating theatre should be air-conditioned with a temperature of between 23 °C and 24 °C. A thermostatically-controlled warm water blanket is placed on the operating table. Before anaesthesia is commenced the diathermy plates are strapped into position, a rectal thermometer is placed and a reliable peripheral line is secured. It is best to place the central venous line, should one be required, when the child is anaesthetised. A Doppler blood pressure apparatus is connected, an ECG monitor is attached to the child and a precordial stethoscope is placed in position. Transcutaneous monitoring devices may also be utilized. Base-line recordings are done and anaesthesia is introduced.

- One of the important factors, during securing of venous lines and preparing the child for surgery is to maintain body-core temperature. This is best done by environmental

temperature control, a warming/cooling blanket, covering the extremities of the baby with warm gamgees, and by the utilization of a radiant heater. The administration of warm humidifying gases and warm fluids at 37 °C may also be indicated. Detrimental effects can be seen if environmental temperature is allowed to fall below an infant's therma neutral zone (29-35 °C) especially depressed metabolic functions and response to stress.

It may also be important during surgery to cover exposed intestine by either warm saline swabs or alternatively it should be placed in a plastic bag to minimize heat and fluid loss.

- Monitoring: Depending on the nature of the operation, constant monitoring of the temperature, pulse, blood pressure, electrolytes, gases, blood glucose concentration and urine output is essential.

- The infant is positioned correctly for the appropriate operation and the operation site is cleaned and painted with povidone iodine in 70% isopropylalcohol. The infant is covered with the usual operating towels including a large steridrape to give protection against infection, to maintain temperature and to keep the baby dry.

- Principles of surgical technique (speed is not essential):

- Conservative surgery

- Meticulous technique

- Gentle and minimal handling of tissue

- Maintenance of aseptic dry field

- Thin monofilament suture material

- Single-layer anastomosis where possible

- Simple mass closure of the anterior abdominal wall and subcuticular skin stitches

- Drain only abscess cavities or large raw surfaces where exceptional drainage is anticipated. Specific anastomosis, i.e. oesophageal atresia may also require drainage.

- Accurate measurement of bloodloss and replacement is mandatory and using a calorimetric method one can accurately measure bloodloss in a baby. Bloodloss in excess of 10% of the estimated blood volume should be replaced with warm blood or stabilized human serum.

- Intraoperative antibiotics may be required.

- The taking of specimens (tissue or fluid) during surgery may become necessary and the adequate disposal thereof is important.

- A light dressing must cover the wound.

- Underwater drainage bottles should be correctly connected.

- A bladder catheter may be required for specific procedures and to monitor urine output.

Guidelines for Fluid Management in Children - Four Basic Principles

(Refer table 3.16.2)

- Maintain normal fluid and electrolyte balance

- Determine the fluid and electrolyte deficit that has resulted from the underlying pathologic process

- Correct these abnormalities:

    - replacement of abnormal losses

    - replacement of ongoing losses

- Monitor the effectiveness of parenteral therapy with reference to maintenance needs, deficits and losses. Adjust the fluid programme accordingly through constant analysis of the patient's response, i.e. weight, sensorium, blood pressure, pulse, perfusion, urine output (minimum 1 mL/kg/h).

Postoperative Care of the Child

Children have specific needs and physiologic limitations. With appropriate regard to the surgical disease, response to resuscitation and surgery and related complications, they usually do well following major surgery. At completion of the operative procedure they are transferred to the ICU or to the ward only when stable or fully recovered from anaesthesia.

Monitoring

Monitoring will depend on the surgical procedures and the status of the child. Vital signs including sensorium, blood pressure, pulse, respiration, CVP, peripheral circulation, transcutaneous oxygen monitoring, daily weight and urine output. These investigations must be done regularly and accurately documented.

Respiratory Care

Supportive respiratory care is an integral part of the perioperative management. To prevent respiratory insufficiency due to immature respiratory mechanisms, pain, inability to clear secretions and microatelectasis, additional oxygen (head box, nasal) may be indicated. Physiotherapy and postural changes may further improve pulmonary function. The need to establish an artificial airway or some mechanism of ventilatory support, must be based on

objective criteria:

pH < 7.30 and $PaCO_2$ > 60 torr

FiO_2 > 60% and PaO_2 < -20 cm water

Maximum inspiratory force < -20 cm water

Vital capacity < 20 mL/kg.